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Time-to-onset of diabetes with everolimus use: analysis of a spontaneous reporting system database

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The incidence of hyperglycemia and diabetes induced by everolimus has been shown in previous studies. Our study analyzed diabetes time-to-onset profiles after everolimus use in patients who underwent transplantation and patients with cancer. Using data from April 2007 to December 2018 in the Japanese Adverse Drug Event Report database, the reports with everolimus were classified according to its use as an immunosuppressant or anticancer drug. The median (25%–75%) days of diabetes time-to-onset in patients who underwent transplantation and patients with cancer were 172 (56–315) and 32 (18.5–57), respectively. There were no significant variations among patients with breast cancer, neuroendocrine tumor, and renal cell carcinoma. By conducting a Weibull shape parameter test, the lower limits of the 95% confidence intervals of the shape parameter β values for the indications of the cancer types were > 1, indicating the wear out failure type profile, whereas those for transplantation data indicated a random failure type profile. The diabetes time-to-onset profiles after everolimus use differed between usage as an anticancer drug and immunosuppressant and there were no significant variations among the type of cancer. It was suggested that the incidence of diabetes should be monitored for 1–2 months in patients with cancer, whereas continuous monitoring is needed in patients who undergo transplantation.

1. Introduction

The mammalian target of rapamycin (mTOR) affects signaling downstream of the phosphatidylinositol 3-kinase/Akt pathway and is involved in controlling the cell cycle, including regulating cellular growth, proliferation, angiogenesis, and survival (Meric-Bernstam et al. 2009). Inhibitors of mTOR have been identified as agents with immunosuppressive, antiangiogenesis, and antitumor effects. Everolimus, an mTOR inhibitor, is employed for the treatment of a number of organ transplantations and cancers at different doses: an oral dose of 1.5 to 3 mg daily for heart, renal, and liver transplantations and oral administration of 10 mg daily for breast, neuroendocrine, and renal cell cancers.

Hyperglycemia associated with mTOR inhibitors appears to be caused by impaired insulin secretion and insulin resistance (Konishi et al. 2019; Tanimura et al. 2019; Blandino-Rosano et al. 2017). In clinical practice, mTOR inhibitors, including everolimus, impair glucose homeostasis and cause conditions ranging from mild glucose intolerance to new-onset diabetes (Morviducci et al. 2018). When used as an immunosuppressant, the incidence of diabetes induced by mTOR inhibitors is higher in combination with calcineurin inhibitors (CNIs) than in combination with other immunosuppressants, as CNIs are also associated with the adverse effect of hyperglycemia (Johnston et al. 2008). When used as an anticancer drug, mTOR inhibitors significantly increase the risk of new-onset diabetes and induce a 5-fold increase in the risk of severe hyperglycemia (Vergès 2018). The risk increase is suggested to be caused by dose increases (Morviducci et al. 2018). In addition, the risk of hyperglycemia attributable to everolimus varies by tumor type (Morviducci et al. 2018; Xu et al. 2018; Vergès et al. 2015).

Recently, spontaneous adverse event reporting systems for time-to-onset analyses have been applied to evaluate the hazard functions for specific adverse events. Practically, using the Japanese Adverse Drug Event Report (JADER) database, the association between hyperglycemia and some drugs, including everolimus, has been reported (Konishi et al. 2019; Fujita et al. 2019), and the incidence of hyperglycemia and diabetes associated with everolimus is widely known. However, studies on diabetes time-to-onset associated with everolimus are scarce, and further research will help determine the appropriate monitoring interventions needed during everolimus treatment. Therefore, the aim of this study was to analyze diabetes time-to-onset profiles after everolimus use in patients who underwent transplantation and patients with cancer.

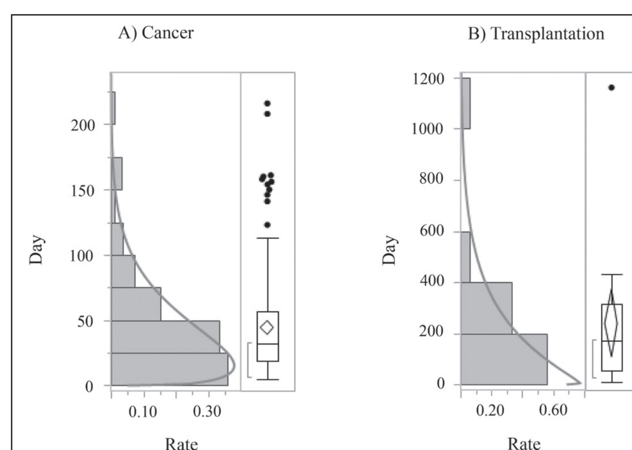

Fig. 1: Histogram of diabetes after everolimus use for A) cancer and B) transplantation.

2. Investigations and results

We identified a total of 3,797 reports that used any of the eight hyperglycemia-related PTs. A total of 8,089 reports were extracted for everolimus. After classifying according to brand name, dose, and reason for use, 2,425 and 5,552 reports were distinguished for everolimus indicated for transplantations and cancers, respectively. We identified 18 of 28 reports on transplantations and 193 of 270 reports on cancer that contained onset time data. The calculated median (25%–75%) time of the diabetes time-to-onset for transplantation and cancer was 172 (56–315) and 32 (18.5–57) days, respectively (Table 1). The histogram of the incidence of diabetes for cancer and transplantation is shown in Fig. 1.

For the three indications associated with different cancer types, 16, 37, and 139 reports containing time-to-onset data for breast cancer, neuroendocrine tumor, and renal cell carcinoma, respectively; the calculated median (25%–75%) time of the time-to-onset was 34.5 (27–50.5), 36 (22–76), and 29 (15–57) days, respectively (Fig. 2). There was no significant difference for time-to-onset diabetes: in comparison of breast cancer with neuroendocrine tumors (P=0.504), breast cancer with renal cell carcinoma (P=0.702), and neuroendocrine tumor with renal cell carcinoma (P=0.205), respectively.

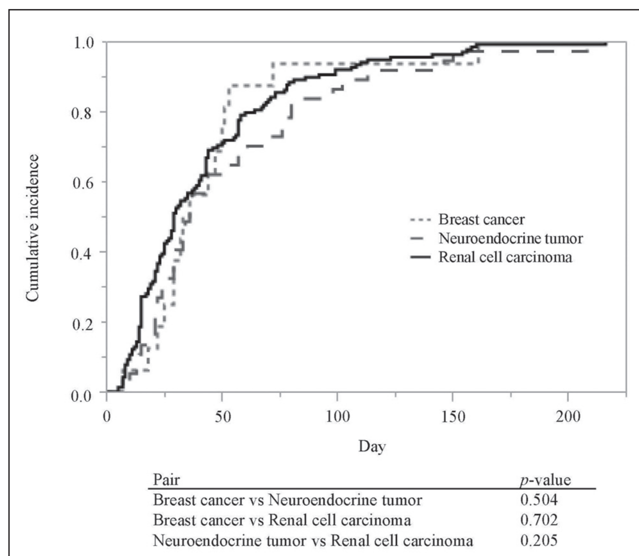

Fig. 2: Cumulative incidence of diabetes after everolimus use in three cancer indications. A *p* value of <0.0167 was considered significant by Log-rank test with Bonferroni method.

The results of the Weibull distribution analysis for the respective indications are provided in Table 1. The scale parameter α value for transplantation and cancer was 241 (144–396) and 48.7 (43.2–54.6), respectively. In all the indications for cancer, the lower limit of the 95% CI of the shape parameter β was > 1, indicating a wear-out failure type profile, whereas an analysis of the transplantation data indicated a random failure type profile.

3. Discussion

In the present study, diabetes time-to-onset profiles after everolimus use in patients who underwent transplantation and patients with cancer were analyzed. The diabetes time-to-onset profiles after everolimus use differed between usage as an anticancer drug and immunosuppressant and there were no significant variations among the type of cancer. By conducting a Weibull shape parameter test, the scale parameter α value for everolimus for cancer types was five times smaller than those for transplantation. In addition, the indications of the cancer types indicated the wear out failure type profile, whereas those for transplantation data indicated a random failure type profile.

In the field of transplantation, Johnston et al. reported that time to new-onset diabetes associated with sirolimus, an mTOR inhibitor, is shorter in patients treated with CNIs than in patients treated with another immunosuppressant (Johnston O et al. 2008). In patients who undergo transplantation, everolimus is typically administered in combination with other immunosuppressants, such as CNIs and corticosteroids, which are commonly associated with the adverse effect of hyperglycemia in clinical practice (Fuhrer et al. 2001). The use of CNIs and corticosteroids increases the risk of new-onset diabetes (Kasiske et al. 2003; David et al. 1980; Knoll et al. 1999) and tacrolimus is associated with a higher risk for new-onset diabetes than cyclosporine (Kasiske et al. 2003; Vincenti et al. 2007). In our study, although 16 corticosteroid- and 13 tacrolimus-treated patients who underwent transplantation received the coadministration of everolimus (data not shown), the time-to-onset of diabetes after everolimus use was longer when used as an immunosuppressant than when used as an anticancer drug (Table 1). Although the background, such as health condition and comorbidities, varied between patients who underwent transplantation and patients with cancer, the time-to-onset of diabetes by everolimus seemed to be attributable to only its dose. Potential hyperglycemia-inducing concomitant drugs did not seem to have a severe influence on the time-to-onset of diabetes.

Generally, everolimus use is beneficial for transplantations. It is used not only to prevent acute rejection that can potentially lead to chronic rejection but also limit CNI-induced nephrotoxicity, protecting against opportunistic cytomegalovirus infection, and inhibit vascular remodeling (Nashan 2001). In this study, the median diabetes onset was 172 (56–315) days of and this was random failure type (Table). As new-onset diabetes is associated with transplant failure (Yilmaz et al. 2015), continuous control of not only planted organs but also glucose levels is required.

The risk of everolimus-induced hyperglycemia has been reported to vary by tumor type (Morviducci et al. 2018; Xu et al. 2016). Among the three cancer indications in this study, renal cell carcinoma had the highest rate, accounting for more than 70%. Although the frequency of adverse events cannot be discussed using the data in the spontaneous reporting system, the reports of the three cancer indications of everolimus-related diabetes in the JADER database showed a trend similar to the findings of previous studies (Morviducci et al. 2018; Xu et al. 2016). On the other hand, the present study suggested that there was no significant difference in the diabetes time-to-onset among the three cancer indications ($p = 0.423$). Therefore, it is suggested that the corresponding time-to-onset duration may not be different, although the incidence of hyperglycemia associated with everolimus varies by type of cancer.

Table 1: Time-to-onset analysis of everolimus-associated diabetes

Indication	Number of cases	Median (25%–75%)	Scale parameter α (95% CI)	Shape parameter β (95% CI)	Type
Transplantation	18	172 (56–315)	241 (144–396)	1.01 (0.69–1.40)	Random failure
Cancer	193*	32 (18.5–57)	48.7 (43.2–54.6)	1.29 (1.16–1.43)	Wear-out failure
Breast cancer	16	34.5 (27–50.5)	49.5 (34.0–70.8)	1.49 (1.02–2.03)	Wear-out failure
Neuroendocrine tumor	37	36 (22–76)	58.4 (44.7–75.5)	1.33 (1.03–1.67)	Wear-out failure
Renal cell carcinoma	139	29 (15–57)	46.0 (39.9–52.8)	1.26 (1.11–1.42)	Wear-out failure

95% CI: 95% confidence interval
*One case lacked a description of indication.

Table 2: Criteria for division of everolimus into the indications for transplantation and cancer in the DRUG table

Indication	Transplantation	Cancer		
		Breast cancer	Neuroendocrine tumor	Renal cell carcinoma
Brand name	Certican		Afinitor	
Dose (/day)	< 3 mg		5 mg – 10 mg	
Primary reason for use	Heart transplantation	Breast cancer male	Gastroenteropancreatic neuroendocrine tumour disease	Clear cell renal cell carcinoma
	Immunosuppressant drug therapy	Breast cancer metastatic	Neuroendocrine carcinoma	Metastatic renal cell carcinoma
	Liver transplantation	Breast cancer recurrent	Neuroendocrine tumour	Renal cancer metastatic
	Prophylaxis against transplant rejection	Inflammatory carcinoma of the breast	Neuroendocrine tumour of lung	Renal cancer recurrent
	Renal transplantation	Invasive ductal breast carcinoma	Pancreatic neuroendocrine tumour	Renal cell carcinoma
	Transplant rejections	Invasive papillary breast carcinoma	Pancreatic neuroendocrine tumour metastatic	Renal cell carcinoma recurrent

Since hyperglycemia and diabetes are associated with greater aggressiveness of many tumors, chronic hyperglycemia may increase the risk progression of cancer by stimulating the mTOR pathway and mitogen-activated protein kinase pathway, thereby promoting tumor assimilation and cell proliferation (Vander Heiden et al. 2009; Vernieri et al. 2016). In this study, the median diabetes onset was 32 (18.5–57) days of and this was wear-out failure type (Table 1). Therefore, health care providers should monitor patients closely for 1 to 2 months.

Our study had some limitations. First, we excluded some data because of the missing dates that made it impossible to calculate the time-to-onset. Second, spontaneous reporting systems have unique limitations, including the lack of details needed to assess causal associations and severity of adverse events, generalized underreporting bias, dependence of the reporting rate on the time of the presence of each drug in the market, exclusion of healthy individuals, and the lack of denominators (van Puijenbroek et al. 2002; Poluzzi et al. 2009). However, using a spontaneous reporting system has many advantages to detect possible drug–adverse event associations, including the availability of information on the coadministration of various drugs and indications in patients, reflecting medical practices (Fujita 2009).

In conclusion, the time-to-onset profiles of diabetes after everolimus use differed between usage as an anticancer drug and an immunosuppressant, where everolimus exhibited a wear-out failure type and random failure type, respectively. The incidence of diabetes with everolimus treatment should be monitored for 1 to 2 months in patients with cancers, whereas continuous monitoring is needed in patients who undergo transplantation.

4. Experimental

4.1. Data source

The JADER data are available for download from the Pharmaceuticals and Medical Devices Agency website (http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp). The database consists of four data sets: patient demographic information, drug information (DRUG), adverse event (REAC), and primary disease. As everolimus was introduced into the Japanese market in March 2007, we used 421,713 of 544,979 reports by excluding those with incomplete/vague age and sex data and limiting the analysis period from April 2007 to December 2018.

4.2. Division of everolimus into respective indications

Extracted everolimus data were divided into the indications for transplantation and cancer by brand name, dose, or reason for use in the DRUG table (Table 2). Cancer was divided further into three specific indications.

4.3. Definition of Diabetes

The adverse events listed in reac are based on the preferred terms (PTs) used in the Medical Dictionary for Regulatory Activities (MedDRA). In our study, the following PTs were used for the definition of diabetes, according to MedDRA/J ver. 22.1: blood glucose increased (PT 10005557), diabetes mellitus (PT 10012601), glucose tolerance impaired (PT 10018429), glucose urine (PT 10018436), glucose urine present (PT 10018478), glycosylated haemoglobin increased (PT 10018484), hyperglycaemia (PT 10020635), and type 2 diabetes mellitus (PT 10067585).

4.4. Cumulative incidence and time-to-onset

The onset time of an adverse event was calculated by adding 1 day to the number of days from the treatment initiation day of the drug of interest until the occurrence of the adverse event using the time information recorded in the JADER database. Therefore, only reports with time-to-onset data were analyzed. After excluding all values greater than the mean plus the two-fold SD values, the median day values with quartiles were calculated for evaluation. Cumulative incidences were plotted using the Kaplan-Meier method and the Log-rank test with Bonferroni adjustment was used for comparison. A p-value of < 0.0167 was considered significant. Furthermore, a Weibull distribution was used to evaluate the adverse event profiles using the Weibull shape parameter test (Sauzet et al. 2013; Yamada et al. 2014; Nakamura et al. 2015; Kinoshita et al. 2019). The Weibull distribution is expressed using the scale parameter α and the shape parameter β. The former represents the scale of the distribution function. It is a quantile where 63.2% of adverse events occur (Sanzet et al. 2013), and large scale values stretch the distribution, whereas small scale values shrink the distribution. The shape parameter β represents the change in a hazard without a reference population over time. There are three failure types based on the value of the shape parameter β: a β value including a 95% confidence interval (CI) < 1 indicates that the hazard increases at an early stage but subsequently decreases (early failure type); a β value equal to or nearly 1 and a 95% CI including 1 indicate that the hazard is constant during the exposure period (random failure type); a β value including a 95% CI > 1 indicates that the hazard increases over time (wear-out failure type). The time-to-onset analysis was performed using the JMP Pro ver. 13.1 software (SAS Institute, Cary, NC, USA).

Conficts of interest: None declared.

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