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ORIGINAL ARTICLE

Predictive factors for the development of diabetes in cancer patients treated with phosphatidylinositol 3-kinase inhibitors

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Abstract

Purpose Targeted therapy using phosphatidylinositol 3-kinase (PI3K) inhibitors is used to treat cancer such as lymphoma. In animal studies, its use raised concern about alteration of glucose metabolism. To date, clinical data are inconclusive; therefore, we investigated the incidence and clinical manifestations of diabetes in cancer patients treated with PI3K inhibitors.

Methods In a retrospective review of diabetes-free patients with advanced solid tumors treated with PI3K inhibitor, we performed Cox regression to identify independent predictors for the development of diabetes.

Results Of 38 patients (mean age: 54.5 years, 23.7% female) having a mean duration of follow-up of 238.5 days who initiated PI3K inhibitors, 55.3% developed diabetes during treatment (mean 29.1 days); among these, 28.6% experienced remission of diabetes after discontinuing PI3K inhibitors (mean 72.1 days). Patients with incident diabetes had higher anti-hypertensive medication use, higher HbA1c levels and fasting glucose at baseline, and longer duration of PI3K inhibitor use ($P=0.024$, $P=0.005$, $P=0.008$, and $P=0.023$, respectively). Previous steroid use and lower baseline HbA1c level were significantly associated with development of diabetes (HR = 8.41, 95% CI 1.89–37.33; HR = 2.16, 95% CI 1.09–4.25, respectively). Patients whose diabetes remitted after discontinuing PI3K inhibitors were younger ($P=0.035$) and had lower fasting glucose levels during PI3K inhibitor treatment ($P=0.001$) compared to those non-remitters.

Conclusions Previous steroid use and lower baseline HbA1c level may be important predictors for developing diabetes in patients with advanced solid tumors treated with PI3K inhibitors, warranting close observation and careful intervention.

Keywords PI3K inhibitor · Cancer · Diabetes · Hyperglycemia

Abbreviations

AKT	Protein kinase B
CI	Confidence interval
BMI	Body mass index
DM	Diabetes mellitus
ECOG PS	Eastern Cooperative Oncology Group performance status
GPCR	G-protein-coupled receptor
HR	Hazard ratio
IFG	Impaired fasting glucose
IGF	Insulin growth factor
IRS	Insulin receptor substrate
mTOR	Mammalian targets of rapamycin
PI3K	Phosphatidylinositol 3-kinase

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PTEN	Phosphatase and tensin homolog
TKI	Tyrosine kinase inhibitor
RTK	Receptor tyrosine kinases

Introduction

Development of medications that block cancer cell growth and survival by specifically interfering with signaling pathways is widely used to treat several cancers [1]. These therapies include the mammalian targets of rapamycin (mTOR) inhibitors, tyrosine kinase inhibitors (TKIs), and phosphatidylinositol 3-kinase (PI3K) inhibitors [2]. The PI3K signaling cascade is activated in human cancers via various mechanisms such as suppression of phosphatase and tensin homolog (PTEN), gain-of-function mutation or amplification of catalytic domain p110α of the class I phosphatidylinositol 3-kinase (PIK3CA), or mutation of protein kinase B (AKT) [3]. As previous studies reported, PI3K dysregulation results in the initiation, proliferation, and maintenance of cancer cells; thus, PI3K inhibitors may play a therapeutic role. Currently, PI3K inhibitors are used to treat chronic lymphocytic leukemia, non-Hodgkin lymphoma, metastatic breast cancer, glioblastoma multiforme, non-small cell lung cancer, and advanced solid tumors [4, 5]. Further PI3K signaling pathway also impacts the mediating effect of insulin on cellular metabolism, so it induces alteration of glucose homeostasis [6–8]. It has been shown that mice lacking p85 in skeletal muscles have impaired PI3K signaling, exhibiting insulin resistance and whole-body glucose intolerance [9]. Furthermore, increased fasting glucose and impaired insulin responsiveness, such as decreased glucose disposal in muscle and non-suppressible hepatic glucose production, were found in mice deficient in AKT2, a signaling molecule downstream of PI3K [10]. Thus, while PI3K signaling amplification is linked to tumorigenesis, attenuation of PI3K signaling downstream contributes to hyperglycemia and diabetes, suggesting that impaired glucose homeostasis may occur in patients treated with PI3K inhibitors. Providers should use caution when using PI3K inhibitors as targeted therapy, as little is known about the clinical course of glucose metabolism during treatment or the predictive characteristics of the development of diabetes. Therefore, in this study, we investigated clinical and metabolic features of cancer patients who develop diabetes after initiating PI3K inhibitor treatment.

Materials and methods

Data collection and measurement of parameters

We performed a retrospective review of medical records of patients with advanced solid tumors including head and neck cancer and breast cancer treated with PI3K inhibitors at the university-affiliated Severance Hospital, Yonsei University College of Medicine, Republic of Korea, from September 2012 to March 2015 and who had follow-up data up to March 2016. We collected: age; sex; cancer type and stage; Eastern Cooperative Oncology Group (ECOG) performance status; family history of diabetes mellitus (DM); current use of anti-hypertensive medication and/or statins; prior use of steroids; body mass index (BMI); levels of HbA1c, fasting glucose, and fasting C-peptide before PI3K inhibitor treatment; PI3K inhibitor dosage; levels of HbA1c and fasting glucose after initiating PI3K inhibitor treatment; presence or absence of development of DM after initiating PI3K inhibitors; anti-diabetic medication use; duration of PI3K inhibitors use; steroid use after discontinuing PI3K inhibitors; and presence or absence of DM remission. The PI3K inhibitor in this study was BMK120, an oral pan-class I PI3K inhibitor. Among 43 patients treated with PI3K inhibitors, 5 were excluded due to a fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%, or use of anti-diabetic medication before PI3K inhibitor initiation, with 38 patients included in the analyses. Incident diabetes and diabetes remission were defined as fasting glucose ≥ 126 mg/dL and fasting glucose level < 126 mg/dL without anti-diabetic medication, respectively. This study was approved by the Institutional Review Board at Severance Hospital (IRB no. 4-2016-0553).

Performance status was according to the ECOG criteria [11]. BMI was calculated as weight divided by height squared (kg/m^2). After an 8-h fast, plasma glucose level was measured by the hexokinase method, and plasma total cholesterol and triglyceride levels were measured using the enzymatic colorimetric method. Serum C-peptide level was measured in duplicate using an immunoradiometric assay method (Beckman Coulter, Fullerton, CA, USA). Plasma total cholesterol and triglycerides were measured using a Hitachi 747 Chemistry Analyzer (Hitachi Ltd, Tokyo, Japan).

Statistical analysis

Continuous and categorical variables were expressed as mean ± standard deviation and proportions, respectively. Comparisons between baseline and follow-up parameters according to presence or absence of incident DM after PI3K inhibitor treatment and presence or absence of incident diabetes remission after PI3K discontinuation were analyzed using Student's *t* test for continuous variables and Chi-squared test for categorical variables. Nonparametric relationships were analyzed using Mann–Whitney *U* tests. We compared HbA1c levels before and after PI3K inhibitor treatment with the paired *t* test. Cox regression analysis was applied to assess whether incident DM after PI3K

inhibitor treatment was associated with various baseline clinical and laboratory parameters. Using Kaplan–Meier survival curves, cumulative event rates for incident DM after PI3K inhibitor treatment were analyzed. Probability values were calculated with the logrank test. All analyses were performed using PASW Statistics for Windows version 20.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered as statistically significant.

Results

Clinical and laboratory characteristics of patients who developed incident diabetes

A total of 38 patients treated with PI3K inhibitors with a mean follow-up duration of 238.5 ± 242.1 days (range 25–945 days) were analyzed in this study. Cancer types were tongue cancer ($n = 9$, 23.7%), tonsillar cancer ($n = 8$, 21.1%), and hypopharyngeal cancer ($n = 7$, 18.4%). All patients had received prior anti-cancer therapy and daily BKM120 (50–300 mg). Baseline clinical and laboratory data according to presence or absence of incident DM after PI3K inhibitor use are presented in Table 1. Mean age was 54.5 ± 11.2 years; 23.7% ($n = 9$) were female. The mean BMI was 20.9 ± 2.9 kg/m^2, and 55.3% ($n = 21$) of patients were defined as having impaired fasting glucose (IFG; ≥ 100 mg/dL). Of 38 patients, 21 (55.3%) developed DM during PI3K inhibitor treatment, and the mean duration from treatment initiation to DM diagnosis was 29.1 ± 18.2 days (range 8–77 days). The mean fasting glucose level at DM diagnosis was 190.2 ± 67.2 mg/dL. As shown in Table 1, age, sex, BMI, ECOG performance status, and family history of DM were similar between the non-DM group and incident DM group. Four patients who developed DM had prior steroid use, but this was not statistically significant (19% vs. 0% in the non-DM group, $P = 0.113$) Patients with incident DM had more hypertension medication compared to non-DM patients (28.6% vs. 0%, $P = 0.024$). Regarding glycemic parameters, baseline HbA1c (5.6 ± 0.3% vs. 5.9 ± 0.3%, $P = 0.005$) and fasting plasma glucose levels (94.6 ± 10.0 mg/dL vs. 104.6 ± 11.3 mg/dL, $P = 0.008$) were significantly higher in subjects with vs. without incident DM. The incident DM group showed a higher proportion of subjects with IFG compared to the non-DM group (76.2% vs. 29.4%, $P = 0.008$). There was no between-groups statistical difference in initial fasting C-peptide, total cholesterol and triglyceride levels or PI3K inhibitor dosage, but the incident DM group had a markedly longer treatment duration

Table 1 Baseline characteristics of patients by incident DM status

	Non-DM cases ($n = 17$)	Incident DM cases ($n = 21$)	*P* value
Age (years)	55.1 (12.09)	54.0 (9.9)	0.774
Female, *n* (%)	5 (29.4)	4 (19.0)	0.703
BMI (kg/m^2)	20.1 (2.9)	21.6 (2.8)	0.929
ECOG performance status, *n* (%)			0.456
0	3 (7.9)	7 (18.4)	
1	13 (34.2)	12 (31.6)	
2	1 (2.6)	2 (5.3)	
Hypertension medication, *n* (%)	**0 (0.0)**	**6 (28.6)**	**0.024**
Statin medication, *n* (%)	0 (0.0)	4 (19.0)	0.113
Family history of diabetes, *n* (%)	3 (17.6)	2 (9.5)	0.640
Prior steroid use, *n* (%)	0 (0.0)	4 (19.0)	0.113
Initial IFG, *n* (%)	**5 (29.4)**	**16 (76.2)**	**0.008**
Initial HbA1c (%)	**5.6 (0.3)**	**5.9 (0.3)**	**0.005**
Initial fasting glucose (mg/dL)	**94.6 (10.0)**	**104.6 (11.3)**	**0.008**
Initial fasting C-peptide (ng/mL)	2.45 (1.44)	3.42 (1.92)	0.141
Initial total cholesterol (mg/dL)	156.2 (43.9)	176.7 (33.1)	0.109
Initial triglyceride (mg/dL)	87.4 (42.3)	103.0 (74.8)	0.448
PI3K inhibitor dosage (mg/day)	140.0 (52.4)	146.2 (69.2)	0.977[†]
Duration of PI3K inhibitor use (days)	**72.4 (100.9)**	**102.2 (90.2)**	**0.023**[†]

Data are presented as mean (standard deviation) or number (percent)

Bold values indicate statistical significance

BMI body mass index, *DM* diabetes mellitus, *ECOG* Eastern Cooperative Oncology Group, *IFG* impaired fasting glucose, *PI3K* phosphatidylinositol 3-kinase

[†]Data are analyzed using Mann–Whitney U tests

(102.2 ± 90.2 days; range: 23–430 days) compared with the non-DM group (72.4 ± 100.9 days; range: 12–435 days; $P = 0.023$). During PI3K inhibitor treatment, the last measured HbA1c was significantly higher in incident vs. non-incident DM group (7.3 ± 1.1% vs. 6.0 ± 0.3%, $P = 0.005$, data not shown). In the non-DM group, HbA1c levels before and after treatment were not significant (0.3 ± 0.4%, $P = 0.113$, data not shown), whereas HbA1c increased significantly by an average of 1.4 ± 1.0% ($P < 0.0001$, data not shown) during the PI3K treatment period.

Demographics and treatment of patients with incident diabetes

Table 2 presents 21 patients who developed incident DM during treatment with PI3K inhibitors. Among them, six (28.6%) showed remission of DM after discontinuing PI3K inhibitor. The duration from discontinuation of PI3K inhibitor to DM remission was 72.1 ± 83.1 days (range 6–229 days). Of 21 patients with incident DM, the majority had tonsillar cancer ($n = 6$, 28.6%), tongue cancer ($n = 4$, 19.0%), and hypopharyngeal cancer ($n = 4$, 19.0%); 85.7% ($n = 18$) were treated with anti-diabetic medication and among them, 6 (33.3%) patients received monotherapy. Of the 18 anti-diabetic medication users, 7 (38.9%) used insulin, 14 (77.8%) used metformin, 6 (33.3%) used thiazolidinediones, and 4 (22.2%) used sulfonylurea.

Clinical characteristics of patients with incident DM by presence or absence of DM remission

Table 3 presents the comparison between those who did vs. did not experience DM remission during the study period. Those in the remission group were significantly younger than those with persistent DM (47.0 ± 10.1 years vs. 56.9 ± 8.6 years, $P = 0.035$). However, there were no significant between-group differences in sex, BMI, baseline HbA1c, fasting glucose, and C-peptide, or PI3K inhibitor use duration. Fasting glucose level at DM diagnosis and the last measured HbA1c level during treatment were insignificantly lower in the DM remission group compared with the persistent DM group. Subjects whose DM remitted had markedly lower fasting glucose levels at last measurement during treatment (180.1 ± 77.2 mg/dL vs. 100.8 ± 9.3 mg/dL, $P = 0.001$). There were no significant differences in previous steroid use or steroid use after PI3K inhibitor discontinuation between the DM remission and DM persistent groups.

Predictive parameters for development of diabetes after PI3K inhibitor initiation

Cox regression analysis was performed to identify baseline predictors for development of DM after initiating PI3K inhibitor treatment (Table 4). Prior steroid use (HR 8.41, 95% CI 1.89–37.33, $P = 0.005$) and higher HbA1c (HR 2.16, 95% CI 1.09–4.25, $P = 0.027$) were significantly associated with DM development after PI3K inhibitor treatment. As shown in Fig. 1, we found a higher cumulative incidence of DM after PI3K inhibitor treatment in subjects with vs. without prior steroid use ($P = 0.003$ by logrank test; Fig. 1a), and in those with HbA1c > 6.1% compared with HbA1c ≤ 6.1% ($P = 0.002$ by logrank test; Fig. 1b).

Discussion

We selected diabetes-free patients who initiated treatment with PI3K inhibitors to assess development of diabetes. Among 38 patients treated with PI3K inhibitors, 55.3% ($n = 21$) developed DM during the PI3K inhibitor treatment period, with mean duration from treatment initiation to DM diagnosis was 29.1 ± 18.2 days (range 8–77 days). Patients who developed DM after PI3K inhibitor treatment had high HbA1c levels and history of steroid use. Among incident DM patients, six (28.6%) revealed DM remission after discontinuing PI3K inhibitor use during the study period. DM remission occurred after an average of 72.1 ± 83.1 days (range 6–229 days) from treatment discontinuation. In addition, patients whose DM remitted were significantly younger and had lower fasting glucose levels during the PI3K inhibitor treatment compared with those whose DM persisted.

PI3K signaling plays a pivotal role in several cellular processes critical for cancer cell growth, proliferation, metabolism, and survival [6, 12]. Genetic alterations in various components of this pathway have been reported to frequently occur in human cancer (e.g., amplification of the PI3KCA gene encoding the p100α catalytic subunit, inactivation of PTEN, mutation of AKT, accumulation of gene coding for the regulatory subunit of PI3K, p85) [13–16]. Consequently, PI3K inhibitor is a promising therapy to treat cancers. BMK120, the PI3K inhibitor in this study, is an oral pan-class I PI3K inhibitor, but with a lower potency against class III and class IV PI3Ks or mTOR [17, 18]. There are three classes of PI3Ks (I–III), with the most important kinase in signal transduction being class I, which is grouped into two subfamilies according to the receptors to which they respond, e.g., growth factor receptor tyrosine kinases (RTKs) for class IA, and G-protein-coupled receptors (GPCRs) for class IB [19, 20]. Class IA PI3Ks are heterodimers composed of a p85 regulatory subunit and a p110 catalytic subunit [3]. Insulin and insulin growth factor 1 (IGF1) receptors use adaptor molecules such as insulin receptor substrate 1 (IRS1) to engage class IA PI3Ks, and p110α predominantly appears to mediate insulin signal transduction [6, 21]. As the PI3K signaling pathway operates downstream of the insulin receptor and IRS adaptor molecules, this also regulates

Table 2 Demographic and clinical characteristics of incident DM patients

Patient no.	Age (years)	Sex	Cancer diagnosis/stage	ECOG PS	Family history of DM	BMI (kg/m^2)	Initial fasting glucose (mg/dL)	Initial HbA1c (%)	Normal/IFG	PI3K inhibitor dosage (mg/day)	PI3K inhibitor treatment duration (days)
1	39	F	Tongue/IV	1	Yes	17.1	106	5.7	IFG	100	43
2	34	M	Tongue/IV	1	No	23.7	112	6.3	IFG	100	57
3	56	M	Tonsil/IV	1	No	22.1	85	5.7	Normal	180	106
4	59	F	Breast/IV	0	No	24.1	109	6.1	IFG	50	170
5	52	F	Breast/IV	0	No	20.5	110	5.5	IFG	100	93
6	42	M	Paranasal sinus/IV	2	No	24.8	100	5.7	IFG	180	69
7	53	M	Tonsil/IV	2	No	23.6	107	5.6	IFG	240	53
8	49	M	Tonsil/IV	1	No	21.6	107	5.8	IFG	100	72
9	61	M	Hypopharynx/IV	0	No	21.6	120	6.1	IFG	100	106
10	52	M	Hypopharynx/IV	1	No	16.8	110	5.5	IFG	300	40
11	60	M	Tonsil/IV	1	No	24.8	106	5.9	IFG	100	161
12	58	M	Tongue/IV	0	No	22.3	116	5.7	IFG	300	63
13	49	M	Ethmoid sinus/IV	1	No	20.0	108	6.4	IFG	180	94
14	53	M	Glottis/IV	1	No	23.4	95	6.2	Normal	100	226
15	46	M	Tonsil/IV	0	Yes	25.2	124	6.2	IFG	180	430
16	53	F	Hypopharynx/IV	1	No	18.4	92	5.3	Normal	180	25
17	58	M	Maxillary sinus/IV	1	No	24.3	100	5.8	IFG	100	59
18	51	M	Tonsil/IV	0	No	16.7	79	5.9	Normal	100	82
19	79	M	Hypopharynx/IV	1	No	20.7	117	6.4	IFG	100	23
20	69	M	Glottis/IV	1	No	18.5	92	5.9	Normal	180	60
21	62	M	Tongue/IV	0	No	23.4	101	5.7	IFG	100	114

Patient no.	Duration from PI3K inhibitor initiation to DM diagnosis (days)	Fasting glucose level at DM diagnosis (mg/dL)	DM medication	Steroid use after PI3K inhibitor discontinuation	Remission of DM	Duration from PI3K inhibitor discontinuation to remission of DM (days)	Follow-up period after PI3K inhibitor discontinuation (days)	Total follow-up period (days)
1	29	197	TZD	No	Yes	6	23	66
2	29	162	Metformin	No	Yes	22	41	98
3	29	174	Metformin, SU	Yes	Yes	28	97	189
4	36	149	Metformin	No	Yes	97	412	582
5	77	141	Metformin, TZD	No	Yes	229	538	615
6	13	256	Insulin, metformin	No	Yes	51	931	945
7	48	164	None	Yes	No	–	14	67
8	58	177	None	Yes	No	–	16	88
9	43	219	Insulin, metformin	No	No	–	48	154

Table 2 (continued)

Patient no.	Duration from PI3K inhibitor initiation to DM diagnosis (days)	Fasting glucose level at DM diagnosis (mg/dL)	DM medication	Steroid use after PI3K inhibitor discontinuation	Remission of DM	Duration from PI3K inhibitor discontinuation to remission of DM (days)	Follow-up period after PI3K inhibitor discontinuation (days)	Total follow-up period (days)
10	11	204	Insulin, metformin, SU	No	No	–	52	92
11	16	226	Metformin, TZD, DPP-4i	Yes	No	–	56	217
12	8	254	Metformin, TZD	Yes	No	–	56	119
13	30	187	Metformin, SU	Yes	No	–	186	280
14	15	356	Metformin, SU	Yes	No	–	253	479
15	15	351 (postprandial)	Insulin, metformin	Yes	No	–	385	843
16	15	224	Insulin, TZD, voglibose	No	No	–	0	25
17	28	236	Insulin	Yes	No	–	17	74
18	54	143	None	No	No	–	25	107
19	13	138	Insulin	No	No	–	32	55
20	30	165	Metformin	No	No	–	34	99
21	15	223	Metformin, TZD	Yes	No	–	35	149

BMI body mass index, *DM* diabetes mellitus, *ECOG PS* Eastern Cooperative Oncology Group performance status, *F* female, *IFG* impaired fasting glucose, *M* male, *PI3K* phosphatidylinositol 3-kinase, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *SU* sulfonylurea, *TZD* thiazolidinediones

Table 3 Clinical characteristics by DM remission status

	Persistent DM ($n=15$)	DM remission ($n=6$)	P value
Age (years)	**56.9 (8.6)**	**47.0 (10.1)**	**0.035**
Female, *n* (%)	11 (73.3)	5 (83.3)	0.053
BMI (kg/m^2)	21.4 (2.8)	22.0 (2.9)	0.660
ECOG performance status, *n* (%)			0.769
0	5 (23.8)	2 (9.5)	
1	9 (42.9)	3 (14.3)	
2	1 (4.8)	1 (4.8)	
Hypertension medication, *n* (%)	5 (33.3)	1 (16.7)	0.623
Statin medication, *n* (%)	2 (13.3)	2 (33.3)	0.544
Family history of diabetes, *n* (%)	1 (6.7)	1 (16.7)	0.500
Initial IFG, *n* (%)	11 (73.3)	5 (83.3)	1.000
Initial HbA1c (%)	5.9 (0.3)	5.8 (0.3)	0.694
Initial fasting glucose (mg/dL)	104.9 (12.1)	103.7 (10.1)	0.823
Initial fasting C-peptide (ng/mL)	3.12 (1.60)	4.16 (2.58)	0.273
Previous steroid use, *n* (%)	4 (26.7)	0 (0)	0.281
PI3K inhibitor dosage (mg/day)	157.3 (73.6)	118.3 (51.5)	0.340[†]
Duration for PI3K inhibitor use (days)	107.2 (103.9)	89.7 (45.6)	0.910[†]
Duration from PI3K inhibitor initiation to DM diagnosis (days)	26.6 (16.7)	35.5 (21.7)	0.424[†]
Fasting glucose level at DM diagnosis (mg/dL)	194.4 (75.9)	179.8 (42.2)	0.665
Last fasting glucose level (mg/dL) during PI3K inhibitor treatment	**180.1 (77.2)**	**100.8 (9.3)**	**0.001**
HbA1c (%) during PI3K inhibitor treatment	7.6 (1.1)	6.7 (0.8)	0.104
Steroid use after PI3K inhibitor discontinuation	9 (60.0)	1 (16.7)	0.149

Data are given as mean (standard deviation) or number (percent)

Bold values indicate statistical significance

BMI body mass index, *DM* diabetes mellitus, *ECOG* Eastern Cooperative Oncology Group, *IFG* impaired fasting glucose, *PI3K* phosphatidylinositol 3-kinase

[†]Mann–Whitney

Table 4 Cox regression analysis for predictors of diabetes development after PI3K inhibitor treatment

Variables	HR (95% CI)	P value
Age (year)	1.01 (0.96–1.06	0.646
Sex (men = 0, women = 1)	0.66 (0.21–2.71)	0.660
BMI (kg/m^2)	0.93 (0.74–1.16)	0.505
Family history of diabetes	0.84 (0.13–5.54	0.853
Prior steroid use	**8.41 (1.89–37.33)**	**0.005**
Initial fasting glucose (mg/dL)	1.03 (0.98–1.08)	0.263
Initial HbA_{1c} (%)[a]	**2.16 (1.09–4.25)**	**0.027**

Bold values indicate statistical significance

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *PI3K* phosphatidylinositol 3-kinase

[a]Initial HbA1c level was *Z*-score transformed

insulin-mediated glucose uptake, membrane translocation of the glucose transporter GLUT4, and glycogen synthesis [6, 20–23].

In this manner, the PI3K signaling cascade plays a central role in insulin-mediated metabolic functions mainly related to insulin sensitivity, so that mice or humans receiving PI3K inhibitors would be expected to show deleterious effects on glucose homeostasis [6, 20]. PI3K inhibitor has been reported to result in hyperglycemia simultaneous with increased release of insulin from pancreatic beta cells, suggesting a decreased sensitivity to insulin [20]. Thus, increased use of PI3K inhibitors has raised awareness of adverse effects on glucose metabolism [24]. The present study investigating independent predictive factors for developing diabetes identified two main findings including prior steroid use and high baseline HbA1c levels. Steroids are known to interfere at several steps in the insulin signaling cascade including IRS1, PI3K, or Akt, and result in decreased insulin-mediated glucose uptake and glycogen synthesis [25, 26]. Previous studies also reported that impaired insulin secretion was induced by steroid therapy in both animal and human trials [27–30]. Further, in kidney transplant patients, early steroid discontinuation led to increased risk of post-transplant DM [31]. Therefore,

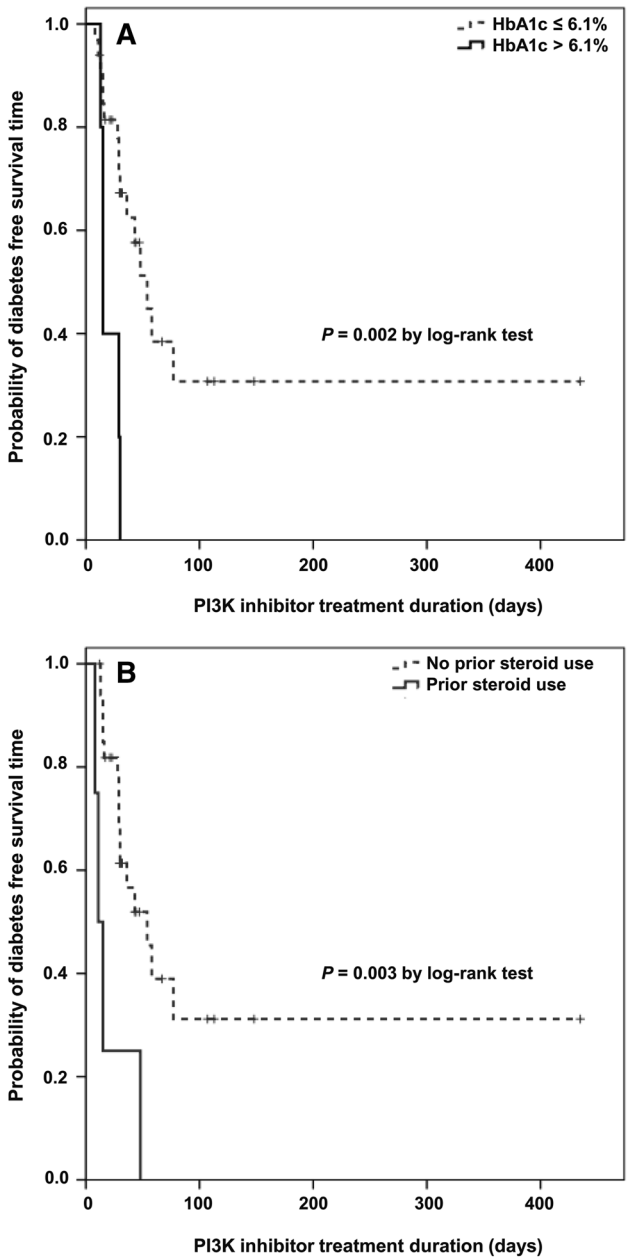

Fig. 1 **a** Kaplan–Meier curves for diabetes-free survival with HbA1c > 6.1% and HbA1c ≤ 6.1%. **b** Kaplan–Meier curves for diabetes-free survival with and without prior steroid use. *PI3K* phosphatidylinositol 3-kinase

patients with previous steroid use or high HbA1c may be vulnerable to insulin resistance, pancreatic beta cell dysfunction caused by PI3K inhibitor treatment, and subjected to develop diabetes [32]. However, we found no correlation between DM development and insulin secretion (C-peptide release). In this study, the incidence of DM is quite high (55.3%) for PI3K inhibitor users, and all newly diagnosed DM occurred during PI3K inhibitor treatment (mean 29.1 days). Collectively this suggests that patients with previous steroid use or high baseline HbA1c levels require close observation, particularly during the month after treatment initiation. In addition, 28.6% of incident DM patients showed remission of DM after PI3K inhibitor discontinuation (mean 72.1 days), particularly in younger and glycemic-controlled (low last-measured blood glucose levels during PI3K inhibitor treatment) patients. Another pan-PI3K inhibitor, PX-866, resulted in hyperglycemia and decreased glucose tolerance, which could be reversed by insulin and pioglitazone, the peroxisome proliferator-activated receptor-γ activator—but not by metformin in an animal study [33]. Moreover, mice treated with pioglitazone, an insulin sensitizer, avoided hyperglycemia caused by PX-866 [34]. However, in this study, we did not find a close relationship between anti-diabetic medication and good glycemic control or DM remission. A large population study will be needed to investigate the association between types of anti-diabetic medications and glycemic control during PI3K inhibitor treatment.

The present study has several strengths. We accessed diabetes-free patients with advanced solid cancer treated with PI3K inhibitors to observe the natural course of glucose metabolism after treatment initiation, during treatment, and after treatment discontinuation; and using Cox regression analysis, we identified predictive factors for developing DM in a real-world setting. Moreover, among patients with incident DM, predictive parameters for DM remission when discontinuing PI3K inhibitors were also investigated in this study, thereby revealing clinical parameters that may predispose to DM and the clinical course of glucose metabolism to be considered by clinicians when treating patients with PI3K inhibitors.

Several points in this study should be addressed in future trials. First, as patients in this study had advanced cancer, follow-up of DM remission was limited by short life expectancy. Moreover, management for hyperglycemia was at the discretion of providers based on clinical judgement. Second, our sample size was relatively small so that predictive factors for developing diabetes regarding beta cell function or insulin resistance may not have been fully estimated. Third, possible changes in lipid metabolism after PI3K inhibitor use were not assessed in this study due to missing related parameters.

In conclusion, we assessed the natural course of glucose metabolism when diabetes-free cancer patients are treated with PI3K inhibitors. History of prior steroid use and a higher baseline HbA1c level at initiation of PI3K inhibitors are clinical parameters that should be considered as important predictive factors for developing diabetes in these patients. Further investigation with a larger study population and a longer study duration is required to better understand the effects of PI3K inhibitors on alteration of glucose metabolism.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest related to this article.

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