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Endocrinology

Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management

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Abstract

Molecularly targeted cancer therapy has rapidly changed the landscape of oncologic care, often improving patients' prognosis without causing as substantial a quality-of-life decrement as cytotoxic chemotherapy does. Nevertheless, targeted agents can cause side effects that may be less familiar to medical oncologists and that require the attention and expertise of subspecialists. In this review, we focus on hyperglycemia, which can occur with use of new anticancer agents that interact with cell proliferation pathways. Key mediators of these pathways include the tyrosine kinase receptors insulin growth factor receptor 1 (IGF-1R) and epidermal growth factor receptor (EGFR), as well as intracellular signaling molecules phosphatidylinositol 3-kinase (PI3K), AKT, and mammalian target of rapamycin (mTOR). We summarize available information on hyperglycemia associated with agents that inhibit these molecules within the larger context of adverse event profiles. The highest incidence of hyperglycemia is observed with inhibition of IGF-1R or mTOR, and although the incidence is lower with PI3K, AKT, and EGFR inhibitors, hyperglycemia is still a common adverse event. Given the interrelationships between the IGF-1R and cell proliferation pathways, it is important for oncologists to understand the etiology of hyperglycemia caused by anticancer agents that target those pathways. We also discuss monitoring and management approaches for treatment-related hyperglycemia for some of these agents, with a focus on our experience during the clinical development of the EGFR inhibitor rociletinib. ***The Oncologist*** 2016;21:1326–1336

Implications for Practice: Treatment-related hyperglycemia is associated with several anticancer agents. Many cancer patients may also have preexisting or undiagnosed diabetes or glucose intolerance. Screening can identify patients at risk for hyperglycemia before treatment with these agents. Proper monitoring and management of symptoms, including lifestyle changes and pharmacologic intervention, may allow patients to continue benefiting from use of anticancer agents.

Introduction

Cancer is the second most common cause of death in the U.S. and Europe after heart disease [1, 2]. In recent years, targeted therapies have delivered important and substantial benefits to patients. These agents inhibit cancer-promoting cellular pathways and can improve overall survival [3]. Compared with traditional cytotoxic chemotherapy, the incidences of low blood counts, severe fatigue, nausea, and vomiting tend to be lower with novel agents; many of these agents have also been associated with improved quality of life [4–9]. Nevertheless, many targeted agents have a side-effect profile that differs from that of traditional chemotherapy. In particular, many newer targeted agents have been found to induce treatment-related hyperglycemia. In this article, we review the agents that are known to cause treatment-related hyperglycemia and provide an overview of monitoring and management for this toxicity (Table 1).

Novel anticancer agents have been developed to target several important cancer characteristics, including sustained proliferative signaling, evasion of growth suppressors, induction of angiogenesis, and avoidance of immune destruction. Sustained proliferation is largely controlled by specific growth and antiapoptotic pathways, notably the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathways. Many of the agents targeting these pathways are small-molecule tyrosine kinase inhibitors, which block ligand-mediated dimerization and activation of downstream effectors. Cell surface receptors can also be inhibited by monoclonal antibodies that interfere with ligand-receptor docking.

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Table 1. Cancer drugs with known side effect of hyperglycemia

		Hyperglycemia across studies	
Targeted therapy type and pathway	**Drug name**	**Range of any grade, %**	**Highest incidence of grade ≥3, %**
Tyrosine kinase inhibitors			
IGF-1R	Cixutumumab [10–13]	17–100	46 [13]
	Dalotuzumab [14, 15]	19–100	32 [15]
	Figitumumab[a] [16–18]	64–100	22 [18]
	Ganitumab[a] [19]	10	NR
	R1507 [20, 21]	5–19	3 [21]
Dual IGF-1R/IR	Linsitinib [22–24]	3–37	5 [23]
Other inhibitors of IGF-1R	Ceritinib [25]	49	13
	Ganetespib [26–29]	0–64	25 [26]
EGFR	Gefitinib [30]	5	NR
	Panitumumab [31]	5	5
	Rociletinib [32]	46	25
PI3K, AKT, and mTOR inhibitors			
PI3K	Buparlisib [33]	31	8
	Pictilisib [34]	2	2[b]
	Pilaralisib [35]	7	0
AKT	Afuresertib[c] [36]	3	0
	GSK2141795[d] [37]	21	5
	Ipatasertib[d] [38]	9	0
	MK-2206[e] [39–41]	8–30	9 [40]
mTOR	Everolimus [42–54]	7–93	22 [53]
	Ridaforolimus [55–57]	11–29	19 [57]
	Temsirolimus [58–66]	7–76	24 [61]
Dual PI3K/mTOR	BEZ235 [67]	24	9
	GDC-0980 [68]	46	46
	PF-04691502 [69]	27	11
	PF-05212384/PKI-587 [70]	26	2
PD-1 inhibitors			
PD-1	Nivolumab [71]	<1	0
	Pembrolizumab [72]	40–48	3

[a]Development discontinued.
[b]Grade 4 specified.
[c]Inhibits AKT1.
[d]Inhibits AKT1, AKT2, and AKT3.
[e]Inhibits AKT1 and AKT2.
Abbreviations: EGFR, epidermal growth factor receptor; IGF-1R, insulin growth factor 1 receptor; IR, insulin receptor; mTOR, mammalian target of rapamycin; NR, not reported; PD-1, programmed death-1; PI3K, phosphatidylinositol 3-kinase.

The body regulates blood glucose levels in several ways. Excess serum glucose increases the secretion of insulin from the pancreatic β cells. The action of insulin begins when the hormone binds to the insulin receptor (IR) in the cell membrane. In addition to promoting cellular uptake of glucose, IR activates intracellular pathways, including PI3K/AKT/mTOR, affecting glucose homeostasis by increasing glycogen synthesis and decreasing glycolysis [73–75]. Insulin growth factor receptor 1 (IGF-1R) is partially homologous to IR and is an important mediator of growth and anabolic effects [76–78]. Activation of IGF-1R via its ligand insulin growth factor 1 (IGF-1) inhibits growth hormone release from the pituitary; high levels of growth hormone promote insulin resistance and increased gluconeogenesis [78]. Increased levels of growth hormone also stimulate hepatic production of IGF-1 as part of a negative feedback loop. Figure 1 illustrates the current understanding of these proteins and their pathway interactions, as well as the targeted cancer therapies that inhibit them.

Hyperglycemia has systemic effects that may result in constitutional symptoms (e.g., fatigue, anorexia, weight loss, polyuria, polydipsia, blurred vision, nausea, diarrhea, dehydration, and renal insufficiency) [73, 74]. If left untreated, these conditions may cause a progressive decline in quality of life and functional status. Even if a patient is deriving antitumor benefit from a targeted agent, onset of constitutional symptoms or other adverse events may lead to dose reductions or treatment discontinuation, potentially resulting in reduced efficacy. By having a good understanding of the etiology of treatment-related

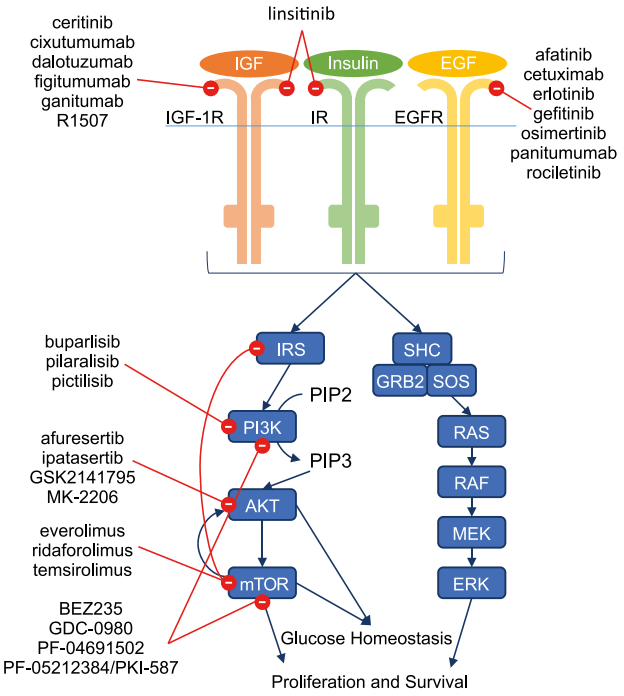

Figure 1. Cellular control of hyperglycemia. Glucose homeostasis is maintained at a cellular level through activation of the intracellular PI3K/AKT/mTOR pathway downstream of IGF-1R and IR. These receptors, along with EGFR, can also activate the Ras/MAPK/ERK pathway, which plays a role in cellular proliferation and survival. Targeted therapies designed to inhibit cancer cell proliferation and promote apoptosis act on these pathways at multiple points (red circles).

Abbreviations: EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; IGF, insulin growth factor; IGF-1R, insulin growth factor receptor 1; IR, insulin receptor.

hyperglycemia and the pathways that are associated with this adverse event, clinicians may be in a better position to manage and mitigate treatment-related hyperglycemia (Fig. 2).

Methods

Published, English-language articles were identified by searching PubMed for the following: ("hyperglycemia" OR "hyperglycaemia") AND ("inhibitor") AND ("tyrosine kinase" OR "PI3K" OR "AKT" OR "mTOR" OR "IR" OR "IGF-1R" OR "EGFR" OR "PD-1"). Results were screened to identify clinical trials of anticancer agents used as monotherapy to avoid confounding factors present in combination studies. Additional information was obtained by reviewing oncology-focused congress abstracts published within the past 10 years and prescribing information for anticancer agents known to cause treatment-related hyperglycemia.

Treatment-Induced Hyperglycemias

IGF-1R Inhibitors

IGF-1R activates the Ras/MAPK/extracellular regulated kinase (ERK) and PI3K/AKT/mTOR pathways, which regulate cell proliferation, inhibit apoptosis, and are associated with other cancer-related processes (Fig. 1) [79]. IGF-1R is a cell surface receptor and, as such, can be targeted by monoclonal antibodies or small molecules. Many IGF-1R inhibitors also block IR as a result of receptor homology [76, 80].

IGF-1R-Specific Monoclonal Antibodies

Monoclonal antibodies that target IGF-1R that are currently in clinical development include dalotuzumab and cixutumumab. Figitumumab, ganitumab, and R1507 were previously under evaluation but their clinical development has been discontinued. Hyperglycemia was listed as a common adverse event (AE) in all but 2 of 12 studies reported in the literature for these agents [10–21]. Other common AEs that have been observed with these agents include fatigue, nausea, and anorexia, which may have been associated with hyperglycemia. The incidence of hyperglycemia for these 5 agents ranged from 10% to 100% (any grade) and from 0% to 46% (grade 3), and appeared to be dependent on dose and the frequency of administration.

In a phase I study of dalotuzumab (10–30 mg/kg weekly) in patients with mixed solid tumors, the overall incidence of hyperglycemia was 19% (1 patient had grade 3 hyperglycemia) [14]. In a small phase II study of patients with neuroendocrine tumors treated with dalotuzumab (10 mg/kg weekly), all patients experienced hyperglycemia; the incidence of grade 3 or greater hyperglycemia was 32% [15].

In several phase I and II studies of cixutumumab for the treatment of mixed solid tumors, hyperglycemia incidence was dose dependent. The incidence of all-grade hyperglycemia ranged from 17% to 100% (5%–46% for grade 3 hyperglycemia) [10–13]. The lowest incidence of hyperglycemia occurred with biweekly administration of cixutumumab (10 mg/kg) [10, 11]. Weekly administration of cixutumumab, even at a lower dose (6 mg/kg), resulted in a notably higher incidence of hyperglycemia [13].

In a study of figitumumab for mixed solid tumors, the rate of hyperglycemia (all grade) was 64% over a range of doses (3–20 mg/kg every 3 weeks) [16]. During the dose-expansion phase of the study, hyperglycemia (all grade) was observed in 100% of patients who received 20 mg/kg of figitumumab; 21% of patients experienced grade 3 hyperglycemia [17]. In both studies, glucose, insulin, and human growth hormone (hGH) were monitored when feasible in patients receiving the 20 mg/kg dose. Elevations in glucose and hGH levels were not clinically significant by the end of each study, but most patients had increased levels of insulin [16, 17]. In a larger study of patients with metastatic colorectal cancer, treatment with 20 mg/kg or 30 mg/kg figitumumab every 3 weeks resulted in rates of hyperglycemia (all grade) of 26% and 33%, respectively; the majority were grade 3 events [18].

Ganitumab was tested in a small phase I study in patients with mixed solid tumors or non-Hodgkin lymphoma [19]. In that study, 10% of 50 nondiabetic patients experienced hyperglycemia.

R1507 was examined in phase I and phase II studies before development was suspended. In the phase I dose-escalation study (dosing range, 1–9 mg/kg weekly) in patients with mixed solid tumors, clinically significant hyperglycemia was only observed in 2 of 37 patients, both of whom had abnormal glucose tolerance at baseline [20]. In a larger phase II study of R1507 in patients with Ewing's sarcoma (9 mg/kg weekly or

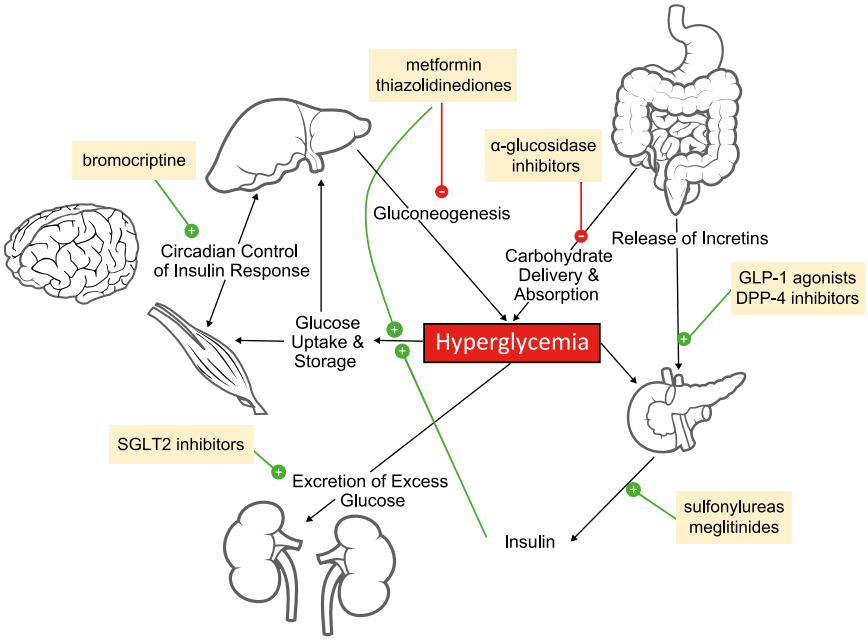

Figure 2. Systemic control of hyperglycemia. Hyperglycemia is controlled systemically (solid black lines) through the release of insulin, which promotes glucose uptake and storage in organs such as the liver and muscles and excretion of excess glucose by the kidneys. Several drugs (yellow boxes) can be used to counteract hyperglycemia, for example, by inhibiting gluconeogenesis or promoting the production of insulin. Stimulatory signals are indicated by green circles containing white "+" symbols, and inhibitory signals are displayed as red circles containing white "–" symbols.

27 mg/kg every 3 weeks), hyperglycemia was a common AE, occurring in 19% (any grade) and 3% (grade 3) of patients [21].

As demonstrated by these studies, the incidence of hyperglycemia is variable with monoclonal antibodies that have activity against IGF-1R. This variability may be partially attributed to the small study sizes and patient heterogeneity. Regardless, hyperglycemia was common across these studies, highlighting the need to actively monitor patients for hyperglycemia following initiation of these therapies.

Small-Molecule Inhibitors of IGF-1R and IR

Given the sequence homology between IR and IGF-1R, small molecules designed to target the kinase domain of IGF-1R can also inhibit signaling through IR. For example, the small molecule linsitinib has demonstrated dual IGF-1R and IR inhibition [76]. In two phase I dose-escalation studies in mixed solid tumors and a placebo-controlled phase III study in patients with locally advanced or metastatic adrenocortical carcinoma, hyperglycemia was a common AE [22–24]. Other common AEs in those studies included nausea, vomiting, and fatigue. Rates of hyperglycemia (all grade), regardless of dose, were 17% and 37% in the 2 phase I studies and 3% in the phase III study. Hyperglycemia generally occurred at the highest doses tested (≥300 mg daily) when administered at more frequent dosing intervals. The phase III study used 150 mg daily as the clinical dose, which may explain the lower incidence of hyperglycemia. Patients with documented diabetes were excluded from the majority of these studies. In a very small cohort of nine diabetic patients in one of the phase I studies, five patients reported grade 1 hyperglycemia; three patients reported transient grade 2 or 3 hyperglycemia. These patients did not require alterations in diabetes medications [22].

Other Inhibitors of IGF-1R

The small molecule ganetespib was selected to inhibit the molecular chaperone Hsp90, leading to degradation of key oncogenic proteins, including IGF-1R, EGFR, vascular endothelial growth factor, c-MET, and human epidermal growth factor receptor 2 (HER2) [26]. In a small, phase I, dose-escalation study in patients with hepatocellular carcinoma, hyperglycemia was listed as a common AE along with diarrhea, fatigue, aspartate aminotransferase elevation, and anemia [26]. Any-grade hyperglycemia was experienced by 64% of patients; grade 3 or 4 hyperglycemia was experienced by 25% of patients. Notably, hyperglycemia was not listed as a common AE in an earlier phase I study of patients with solid malignancies nor in larger phase II studies in non-small cell lung cancer (NSCLC) and breast cancer [27–29].

Ceritinib is a small-molecule inhibitor of anaplastic lymphoma kinase, which is frequently mutated in lung cancer and has also been shown to inhibit IGF-1R [25]. In a phase I trial, in which the majority of patients had NSCLC, gastrointestinal AEs including diarrhea, nausea, vomiting, and abdominal pain were the most common side effects; the incidence of hyperglycemia was 49% (all grade) and 13% (grade 3 or 4) [25].

EGFR Inhibitors

The tyrosine kinase receptor EGFR is not directly involved in glucose metabolism. Hyperglycemia following use of EGFR inhibitors, including gefitinib, panitumumab, erlotinib, afatinib, cetuximab, and osimertinib, is uncommon [30, 31, 81, 82].

Rociletinib is a third-generation EGFR tyrosine kinase inhibitor that targets the most common EGFR-activating mutations (L858R and del19) and the acquired primary resistance mutation T790M [83]. In a phase I/II dose-escalation study, treatment-related hyperglycemia (all grade) was reported

in 46% of patients who received rociletinib [32]. Nausea, fatigue, and diarrhea were the other most common AEs. The incidence of hyperglycemia was dose dependent; it was reported in 35%, 45%, 59%, and 67% of patients who received 500, 625, 750, or 1,000 mg b.i.d., respectively [32]. Hyperglycemia was the most common grade 3 event irrespective of dose.

In preclinical NSCLC models, IGF-1R and IR signaling are believed to be among the mediators of resistance to EGFR inhibitors. In the rociletinib TIGER-X study, hyperglycemia was not expected before the onset of the study because rociletinib had no effect on glucose levels in preclinical toxicology studies or an oral glucose tolerance test in the rat. In humans, rociletinib has three major metabolites: M460, M502, and M544. Interestingly, rociletinib has a differential metabolic profile in humans compared with rodents. As such, low levels of M460 and M502 are observed in rodents, whereas higher levels are observed in humans. These metabolites were found to have activity against IGF-1R and IR; thus, the rociletinib-induced hyperglycemia observed in patients likely results from inhibition of these pathways by M460 and M502, and not from the parent molecule itself.

PI3K, AKT, and mTOR Inhibitors

Downstream effectors of IGF-1R and EGFR include PI3K, AKT, and mTOR (Fig. 1). These intracellular mediators can only be inhibited through use of small molecules. Agents that target the PI3K/AKT/mTOR pathway are intended to interfere with cancer cell growth and survival; however, inhibition of this pathway may also lead to hyperglycemia by interrupting the intracellular response to insulin, causing decreased glucose transport, decreased glycogen synthesis, and increased glycolysis (Fig. 1) [73–75]. Activation of AKT via PI3K inhibits nuclear localization of the transcription factor FoxO1, preventing transcription of genes involved in gluconeogenesis. AKT is also involved in activation of glucose transport into the cells and glycogen synthesis. AKT is required for mTOR activation, which plays a key role in nutrient sensing of the cell. Glucose metabolism is mediated by mTOR through activation of hypoxia-inducible factor 1α, a transcription factor that upregulates expression of glucose transporters and glycolytic genes. Chronic inhibition of mTOR has been linked to decreased proliferation and destruction of insulin-producing pancreatic β cells, as well as the development of insulin resistance [84].

PI3K Inhibitors

The PI3K inhibitors currently in early clinical development include pilaralisib, pictilisib, and buparlisib, which inhibit the kinase activity of all PI3K isoforms by preventing binding with adenosine 5′-triphosphate. The most common AEs observed with PI3K inhibitors include rash, nausea, and diarrhea; the incidence of hyperglycemia reported in the literature has generally been low [33–35]. In phase I dose-escalation studies of pilaralisib and pictilisib, less than 8% of patients were reported to have hyperglycemia [34, 35]. In a phase I dose-escalation study of buparlisib in patients with advanced solid tumors, the incidence of hyperglycemia (all grade) was higher (31%), and 8% of patients experienced grade 3 or 4 hyperglycemia [33]. Three of four patients receiving the highest dose (150 mg) experienced hyperglycemia (all grade). The buparlisib study excluded diabetic patients, and managed symptoms with standard antidiabetic therapies.

AKT Inhibitors

The AKT1, AKT2, and AKT3 isoforms share partial sequence homology, and inhibitors in development target some or all of the isoforms. The incidence of hyperglycemia in phase I studies was generally lower with agents specific for one or two isoforms than with agents that inhibit all three isoforms. Other common AEs associated with AKT inhibitors include rash, fatigue, nausea, vomiting, and diarrhea. In a phase I study of the AKT1-specific inhibitor afuresertib for the treatment of multiple myeloma, any-grade hyperglycemia was reported in $<$3% of patients treated across the range of doses tested [36]. MK-2206, an agent that targets AKT1 and AKT2, has been investigated in phase I and phase II studies. In the phase I study, patients with advanced solid tumors treated with 60 mg every other day experienced infrequent ($<$8%) grade 1 or 2 hyperglycemia [39]. In phase II studies with MK-2206, the incidence of hyperglycemia was 10% (2 of 21 subjects; both events grade 3) in patients with nasopharyngeal carcinoma (200 mg/week) [40] and was more frequent (30%) in patients with advanced gastric cancer (60 mg every other day) [41]. Hyperglycemia (all grade) was observed in 9% and 21% of patients, respectively, in phase I dose-escalation studies of ipatasertib and GSK2141795, both of which target the 3 AKT isoforms [37, 38]. Notably, most of the aforementioned studies excluded patients with high fasting blood-glucose (FBG) levels.

mTOR-Specific Inhibitors

With mTOR inhibitors, the incidence of hyperglycemia (all grade) ranges from as low as 7% to as high as 93%, and the incidence of grade 3 or 4 hyperglycemia is generally higher with mTOR inhibitors than with AKT or PI3K inhibitors. An important caveat is that exclusion of patients with diabetes or those with uncontrolled glucose levels was not consistent across studies or agents. Other common AEs observed with mTOR inhibitors include rash, diarrhea, fatigue, stomatitis, anemia, asthenia, and anorexia. In this review, we discuss the mTOR inhibitors temsirolimus, everolimus, and ridaforolimus, which are analogs of rapamycin, the first mTOR inhibitor discovered. These agents bind to both mTOR and a key coactivator, FKBP12, inducing a conformational change that prevents binding of raptor, which is required for activation of downstream signaling molecules (including 4EBP1 and S6K1) [85].

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Everolimus is approved as a monotherapy in the U.S. for treatment of pancreatic neuroendocrine tumors (PNETs),

Table 2. Summary of guidelines for management of hyperglycemia proposed by Busaidy et al. [73] and Villadolid et al. [82]

Patient type	Management guidelines
Patients with no history of diabetes	
Screening and monitoring	- Check glucose (fasting or random) at baseline and every visit
	- Hemoglobin A1c testing is recommended
	- Counsel patients on signs and symptoms of hypo- and hyperglycemia
	- Recommend goal of FBG <160 mg/dL and/or hemoglobin A1c ≤8%
	- High-risk patients (e.g., BMI >25 or family history of diabetes) should perform daily home blood-glucose monitoring during cycle 1, week 1
	- Recommend glucose monitoring 2–3 times per week in cycles 2 and 3 OR on the first day of cycles 2+ and at the end of treatment visit
	- Providers should be contacted if home glucose levels are consistently >160 mg/dL
	- Increase frequency of monitoring in patients experiencing grade ≥1 hyperglycemia
Management of hyperglycemia by grade[a,b]	
Grade 1 (FBG >125–160 mg/dL)	- Once-daily home glucose monitoring
	- Therapeutic lifestyle changes
	- If indicated, treat with metformin (first line), insulin, or sulfonylureas
Grade 2 (FBG >160–250 mg/dL)	- Twice-daily home glucose monitoring
	- Therapeutic lifestyle changes
	- Begin metformin
	- If FBG >200 mg/dL after 2 weeks, add second-line antihyperglycemic (e.g., sulfonylurea, DPP-4 inhibitor, glitazone, meglitinide, SGLT2 inhibitor, α-glucosidase inhibitor, or GLP-1 agonist)
	- Add insulin if FBG >160 mg/dL after 1 additional week
	- If required, stop oral agents, begin insulin injections (4/day)
	- Consider holding agent 48–72 hours if symptomatic
Asymptomatic grade 3 (FBG >250–500 mg/dL)	- Twice-daily home glucose monitoring
	- Begin metformin, consider adding second-line antihyperglycemic
	- Add insulin if FBG >160 mg/dL after 1 week
	- If FBG >160 mg/dL after 1 additional week, stop oral agents, add premeal insulin, monitor glucose before meals and bedtime
Symptomatic grade 3 (FBG >250–500 mg/dL) or asymptomatic grade 4 (FBG >500 mg/dL)	- Consider intravenous fluids
	- Begin metformin, consider adding second-line antihyperglycemic
	- Monitor glucose before meals and bedtime
	- After 1 week, if FBG >250 mg/dL, hold agent
	- Restart when FGB <250 mg/dL and patient has no symptoms
	- Diabetes specialist consultation
Symptomatic grade 4 (FBG >500 mg/dL)	- Hold agent until resolution
	- Begin metformin and second-line antihyperglycemic
	- Consider intravenous fluids
	- Consider diabetes specialist consultation if not controlled by oral agents
	- Consider postprandial or continuous glucose monitoring
Patients with history of diabetes	
Screening and monitoring	- Monitor blood glucose as done before start of treatment
	- Increase frequency of monitoring if blood sugars are above goal
Recommendations based on management at start of treatment	
Lifestyle changes only	- Begin metformin
	- Follow recommendations as for patients without diabetes
FBG >160 mg/dL with oral agents	- Consider adding second oral agent or insulin
	- Follow recommendations as for patients without diabetes
FBG >160 mg/dL with insulin	- Consider multiple-dose insulin and diabetes consultation
	- Monitor glucose before meals and bedtime

[a]Transient grade 1, grade 2, or asymptomatic grade 3 hyperglycemia does not require treatment.
[b]Management of hyperglycemia should be dictated based on specific anticancer agent and patient history; refer to Busaidy et al. [73] and Villadolid et al. [82] for further details.
Abbreviations: BMI, body mass index; DDP-4, dipeptidyl peptidase 4; FBG, fasting blood glucose; GLP-1, glucagon-like peptide 1; SGLT2, sodium/glucose cotransporter 2.

advanced renal cell carcinoma (RCC), renal angiomyolipoma associated with tuberous sclerosis complex, and subependymal giant cell astrocytoma (SEGA). It is also approved in combination with the aromatase inhibitor exemestane for the treatment of hormone receptor-positive, HER2-negative breast cancer. As a combination therapy, this was not included in our review. In phase II and III studies of patients with PNET treated with everolimus (10 mg daily), the incidence of all-grade drug-related hyperglycemia ranged from 12% to 25% [42–44]. Hyperglycemia was among the major grade 3 or 4 drug-related AEs in these studies (range, 5%–18%). The phase III study excluded patients with uncontrolled blood glucose. Phase II and III studies with everolimus in patients with RCC reported a higher incidence of hyperglycemia at any grade (range, 50%–58%) than studies in patients with PNET, whereas grade 3 to 4 hyperglycemia was similar (range, 8%–12%) [45, 46]. In a phase II trial of patients with renal angiomyolipoma, fasting hyperglycemia (any grade) was reported in 14% of everolimus-treated patients; no grade 3 or 4 events were observed [86]. In phase II studies of patients with advanced urothelial cancer, advanced gastric cancer, metastatic pancreatic cancer, and bone or soft-tissue sarcomas, the incidence of hyperglycemia at any grade ranged from 66% to 93% [47–50]. In phase I studies of patients with advanced solid tumors, drug-related hyperglycemia was generally reported in $<$10% of patients [51, 52]. The incidence of hyperglycemia was 48% in patients with hepatocellular or hematologic malignancies [53, 54]. Hyperglycemia was not observed during the phase I/II or phase III trials of patients with SEGA [87, 88]; however, in a long-term follow-up of patients from the phase III trial, 14% reported hyperglycemia [89].

Activated T cells target cancerous cells but can also attack noncancerous normal tissues. This may lead to autoimmune destruction of pancreatic islet cells. Consequently, type 1 diabetes mellitus can occur, leading to decreased insulin levels and hyperglycemia.

Temsirolimus is approved in the U.S. for treatment of advanced RCC. The incidence of drug-related hyperglycemia in studies of patients with RCC treated with temsirolimus (25 mg weekly) ranged from 19% to 27% (all grade) and from 3% to 14% (grade 3 or 4) [58–60]. In phase II studies of patients with other cancers, including castration-resistant prostate cancer, metastatic breast cancer, advanced neuroendocrine cancer, glioblastoma, and NSCLC, rates of hyperglycemia (all grade) ranged from 7% to 76% [61–66]. The difference in rates of hyperglycemia for these studies was not dose dependent; surprisingly, the highest and lowest rates of hyperglycemia were observed with the lowest (25 mg/week) and highest (250 mg/week) doses, respectively [61, 66].

In studies of the mTOR inhibitor ridaforolimus, overall rates of all-grade hyperglycemia (11%–29%) in phase II and III studies were similar to those observed for everolimus and temsirolimus [55–57].

Dual PI3K/mTOR Inhibitors

PF-04691502, PF-05212384/PKI-587, and BEZ235 are molecules that target the catalytic domains of both PI3K and mTOR, which are structurally similar. Dual inhibition may be a valuable strategy because PI3K activity can be upregulated following mTOR inhibition [85]. In phase I studies of nondiabetic patients with solid tumors treated with these agents, the incidence of hyperglycemia (all grade) was in the range of 24%–27% (grade 3, 2%–11%) [67, 69, 70]. GDC-0980, another dual PI3K/mTOR inhibitor, was associated with grade 3 or 4 hyperglycemia in 46% of patients with endometrial cancer in a phase II trial [68]. Other common AEs with dual PI3K/mTOR inhibitors include fatigue, diarrhea, decreased appetite, nausea, rash, mucositis, vomiting, and constipation.

PD-1 Inhibitors

Pembrolizumab and nivolumab, antibodies that target the programmed death-1 (PD-1) receptor, are immune checkpoint inhibitors that promote T-cell activation and proliferation [90, 91]. Activated T cells target cancerous cells but can also attack noncancerous normal tissues [90, 91]. This may lead to autoimmune destruction of pancreatic islet cells. Consequently, type 1 diabetes mellitus can occur, leading to decreased insulin levels and hyperglycemia [90–92]. In phase I studies of pembrolizumab in patients with metastatic melanoma or NSCLC, the incidence of hyperglycemia (all grade) was 40% and 48%, respectively (grade 3, 2%; grade 4, 3%) [72]. Most likely, very few of the hyperglycemic events in this study represented an autoimmune diabetes; the others may have been from concomitant medications such as glucocorticoid medications. Diabetes mellitus was also reported in 1 of 206 patients in a phase III trial of nivolumab for the treatment of metastatic melanoma [71].

Screening, Monitoring, and Management

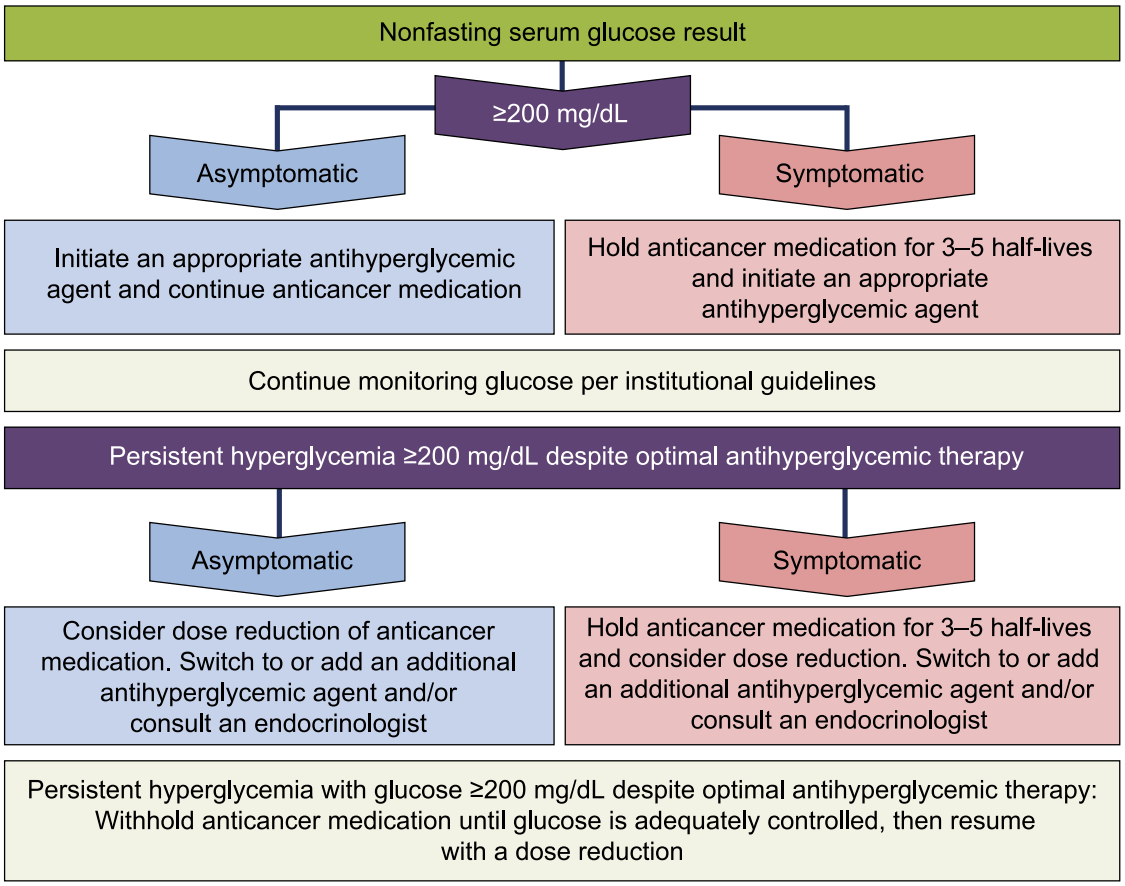
Hyperglycemia may negatively affect patient quality of life and interfere with treatment through dose reductions, delays, and discontinuations; however, the exact effect of hyperglycemia on treatment is often unclear because not all studies report detailed reasons for treatment interruptions. Because of these potential consequences, it is important for treating physicians to adequately screen patients, monitor glucose levels, and manage hyperglycemia as suggested in recently published guidelines (Table 2) [73, 82]. Although these guidelines represent the standard treatment for hyperglycemia, agents that cause severe insulin resistance or block IR may benefit from the treatment algorithm shown in Figure 3. Treating physicians can also work closely with an endocrinologist to ensure that hyperglycemia is being monitored and managed optimally.

Approximately half of the studies discussed thus far screened patients before treatment and excluded patients with preexisting diabetes mellitus or increased blood-glucose levels [10–15, 19–24, 33, 36, 39, 41, 42, 47, 48, 54, 62, 67–70]. In real-world clinical practice, patients who need anticancer treatment may present with preexisting or undiagnosed diabetes and glucose intolerance; screening patients for those conditions could help indicate which patients may require close monitoring.

Monitoring blood glucose levels

- Monitor serum or urine glucose levels approximately weekly during the first 1–2 months and then monthly, or as clinically indicated, while on treatment
- More frequent monitoring may be necessary for patients who experience grade 3 or 4 hyperglycemia or for patients who have diabetes

Management of hyperglycemia



Appropriate antihyperglycemics (categorized by mechanism of hyperglycemia)

- For IR/IGF-1R inhibitors: IR sensitizers (e.g., metformin) or an SGLT2 inhibitor
- Other: insulin sensitizer, secretagogues, an SGLT2 inhibitor, or insulin

Figure 3. Algorithm for management of severe/persistent hyperglycemia. This algorithm, adapted from the protocol used in the TIGER-X study of rociletinib, may be applicable for use with other anticancer agents.

Abbreviations: IGF-1R, insulin growth factor receptor 1; IR, insulin receptor; SGLT2, sodium/glucose cotransporter 2.

During treatment, patients can be monitored for hyperglycemia (with fasting and/or postprandial blood-glucose levels and periodic hemoglobin A1c testing) and for insulin resistance (with insulin levels). Specific monitoring for hyperglycemia was common in many of the previously described studies, especially in studies of IGF-1R inhibitors [13, 16, 17, 19, 20, 33, 41, 62, 69]. Monitoring of all patients is of particular importance because patients considered low risk can still develop hyperglycemia. Additionally, although some agents have been associated with dose-dependent incidences of hyperglycemia, others (e.g., temsirolimus) have not.

Mild treatment-related hyperglycemia may be sufficiently managed through modifications in diet and exercise. Management of grade 3 and 4 hyperglycemia may involve dose reductions and/or the use of oral antihyperglycemic agents (Table 2; Fig. 2) [73, 93]. Insulin and insulin secretagogues are typically suitable options. These agents are used to increase cellular uptake of glucose. For patients who develop type 1 diabetes mellitus following treatment with PD-1 inhibitors, use of insulin is recommended [72]. Exceptions to the use of insulin should be made for patients who are receiving agents that inhibit IR (e.g., linsitinib or the M502 metabolite of rociletinib). In those instances, hyperglycemia should be managed with agents that decrease insulin resistance (e.g., metformin and thiazolidinediones) and increase glucose excretion (e.g., sodium-glucose linked transporter 2 inhibitors). Insulin and insulin secretagogues are unlikely to improve symptoms related to abnormal blood-glucose levels in this setting. Insulin sensitizers are not associated with hypoglycemia.

In many of the aforementioned studies, dose reductions and use of antihyperglycemic agents were sufficient to manage hyperglycemia; very few patients discontinued study drugs because of hyperglycemia [12, 13, 15, 19, 33, 45, 48, 53, 67, 70, 94]. In the rociletinib TIGER-X study, a specific protocol was implemented to manage M502-driven hyperglycemia. For FBG of >200 mg/dL, asymptomatic and symptomatic patients received an oral antihyperglycemic medication. Additionally, rociletinib was held for 48–72 hours in symptomatic patients. Once the drug was held, glucose levels tended to normalize within 24 hours and treatment could be reinitiated. This strategy may also be applicable with other anticancer agents associated with insulin resistance or those that block IR; this simplified management algorithm is provided in Figure 3.

Conclusion

In recent years, a better understanding of the cellular processes that drive cancer growth and survival has prompted the development of agents that target mediators of these processes, including IGF-1R, EGFR, PI3K, AKT, and mTOR. Many of these proteins are also involved in regulating glucose metabolism, and hyperglycemia is a recognized side effect of several targeted agents. Many clinical trials of these targeted agents exclude diabetic patients; however, in a real-world setting, a proportion of patients with cancer may also have preexisting conditions, including hyperglycemia and diabetes mellitus [95]. Screening in advance of treatment could help clinicians identify patients who will need closer observation. Proper hyperglycemia monitoring and management may ultimately lead to more successful outcomes with the use of these anticancer agents.

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