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Review

Effect of New Oncological Therapies on Glucose Metabolism

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Abstract: Targeted cancer therapies and immunotherapy significantly impact glucose metabolism. Tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib have demonstrated beneficial effects by improving glycemic control and preserving pancreatic β-cell function. However, glycemic outcomes vary among TKIs; for example, nilotinib has been associated with impaired glucose regulation, while multikinase inhibitors produce heterogeneous metabolic effects. In contrast, mTOR inhibitors (everolimus, temsirolimus) frequently induce hyperglycemia through complex disruptions of insulin signaling pathways and β-cell functionality. Immune checkpoint inhibitors (ICIs) enhance anti-tumor immune responses by blocking CTLA-4 and PD-1 pathways but can compromise immune tolerance, leading to immune-related adverse events (irAEs). Among these, ICI-induced diabetes mellitus (ICI-DM) is a rare yet severe autoimmune disorder characterized by rapid pancreatic β-cell destruction, often presenting as diabetic ketoacidosis. Unlike the predominantly insulin-resistant diabetes mellitus associated with TKIs and mTOR inhibitors, ICI-DM resembles insulin-dependent type 1 diabetes mellitus and necessitates urgent insulin therapy and vigilant glucose monitoring. Management strategies differ accordingly: TKIs and mTOR inhibitor-induced hyperglycemia are typically addressed with first-line oral agents such as metformin, while ICI-DM requires immediate initiation of insulin treatment. Early recognition and interdisciplinary collaboration with metabolic disorders specialists are critical to preventing severe metabolic complications and allowing continuation of oncologic therapies. Further investigation is warranted to elucidate the precise molecular mechanisms driving these glucose metabolism disturbances and to optimize therapeutic approaches in cancer patients receiving targeted treatments.

Keywords: adverse event; diabetes mellitus; tyrosin kinase inhibitors; mTOR inhibitors; immune-checkpoint inhibitors

1. Introduction

Many novel anticancer therapies, such as tyrosine kinase inhibitors, mTOR inhibitors and immunocheck point inhibitors, currently approved with a view to increasingly personalized medicine, demonstrated to be highly effective in the cure of several cancer type, improving the overall survival (OS) and progression-free survival (PFS). The use of many of these drugs is burdened by several adverse events including metabolic and endocrine side effects.

The hyperglycemia and/or diabetes mellitus are due to the interaction of these drugs with pathways involved in glucose homeostasis and, on the other hand, the control of glycemia is essential in oncological patients because

it is considered a potentially driving force in cancer progression, contributing to the proliferation of tumor cell lines in colorectal, breast and bladder cancer [1]. Hyperglycemia may negatively interfere with the oncological therapies through dose reduction, or delay or discontinuation but the real effect of hyperglycemia is often unclear because the reasons of treatment interruption are not reported in detail in all studies.

Since some oncological treatments are essential, given the lack of alternative therapies in some cases, and although some studies have discussed the possibility of excluding patients with pre-existing diabetes mellitus from cancer therapies, the most appropriate approach is to carry out adequate metabolic screening of these patients before starting oncological treatment and to closely monitor them, especially during the first weeks, in order to ensure early intervention for diabetes as an adverse effect. While hyperglycemia is a well-recognized adverse effect of TKI, mTORi, and ICI therapies, the underlying mechanisms and management strategies are often conflated in the literature. This review aims to clearly delineate the distinct pathogenic mechanisms underlying hyperglycemia induced by these three classes of drugs and to outline optimal therapeutic approaches for each, thereby facilitating more effective clinical management of this adverse event.

2. Materials and Methods

We performed a search of published English articles on the Pubmed database with the following keywords: “diabetes mellitus”, “glycemia”, “cancer”, “tyrosinkinase inhibitors”, “mTOR inhibitors”, “everolimus”, “immune-checkpoint inhibitors”, “immunotherapy”, “AKT and PI3 inhibitors” and “enfortumab”. We considered all the articles that reported the effects of the above-mentioned molecules and anticancer drugs on glucose metabolism and the risk of diabetes mellitus. This review was conducted according to the SANRA scale for the quality assessment of narrative review [2].

3. Tyrosin Kinase Inhibitors (TKIs)

TKIs are currently widely used in the treatment of malignant diseases, ranging from hematological cancers to solid tumors, such as gastrointestinal, lung, and breast cancers, as well as neuroendocrine or advanced-stage thyroid cancers.

As suggested by their name, TKIs are specific inhibitors of tyrosine kinases, particularly inhibiting tyrosine kinase receptors, that are transmembrane receptors activated by a specific ligand. These receptors enable the activation of a downstream cascade capable of triggering crucial mechanisms related to cell survival, duplication, and proper cellular function. The activity of these receptors is tightly controlled in healthy tissues; however, in tumors, this control is often lost, leading to uncontrolled activity of tyrosine kinase receptors, which promotes tumor survival, angiogenesis, epithelial-mesenchymal transition, and other key patterns of tumorigenesis. The tyrosine kinase receptor family consists of 58 members, so, the mutated receptor targets and, therefore, the potential targets for TKIs are numerous. Currently, the most common targets for marketed TKIs include: rearranged during transfection (RET), C-KIT, platelet derived growth factor receptor (PDGF), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and FMS-like tyrosine kinase 3 (FLT3). In this way, pathways such as the MAPK cascade or the mTOR pathway, crucial for cell survival, are blocked in tumor [3].

3.1. Adverse Events and Conflicting Effect on Glucose Metabolism (Table 1)

The use of TKIs over time has been associated to several adverse effects, particularly at the gastrointestinal, cardiac and dermatological levels [4]. Regarding the relationship between TKIs and glucose metabolism, since the beginning of their debuts, several case reports have pointed out that these drugs may have positive effects on diabetes mellitus, improving glycemic control and reducing the need for hypoglycemic medications. These findings have been surprisingly observed in patients with Type 2 Diabetes [5,6] as well as in patients with Type 1 Diabetes, where improvements in serum C-peptide levels have also been noted [7,8]. Subsequently, retrospective studies have confirmed that patients taking TKIs experienced episodes of hypoglycemia as well as reductions in mean glucose levels and HbA1c [9,10].

These findings have been further supported by in vitro studies or animal model. Imatinib reduced diabetes symptoms in two mouse models by partly preserving beta-cell mass and protected human beta-cells from death caused by toxic factors in vitro; this effect involved c-Abl inhibition and activation of NF-kappaB, which is crucial for imatinib’s protective action. Overall, imatinib supports beta-cell survival, contributing to its positive effects in diabetes [11]. GNF-2 and GNF-5 that are selective non-receptor tyrosine kinase inhibitors effective against imatinib-resistant mutations in leukemia, have been studied in mice previously treated with streptozocin (STZ) commonly associated with pancreatic β-cells damage. GNF-2 and GNF-5 has been demonstrated to prevent β-cell

loss, lower blood glucose, and increase insulin levels in mice after STZ treatment [12]. The molecular mechanisms underlying these effects are not entirely clear; however, various possibilities have been suggested. It is important to note that several molecules are now available commercially, targeting different pathways, and some inhibitors on the market are considered multikinase inhibitors so is more difficult to underline a unique mechanism.

Among the most studied targets of TKIs for diabetes control is c-Abl, which plays a significant role in the downregulation of insulin gene expression and in promoting beta-cell apoptosis [13]. It thus becomes evident why its inhibition may be correlated with a benefit on blood glucose level. Other important targets include VEGFR and C-KIT, which, when dysregulated (as occurs in cancer), increase the risk of damage to pancreatic islets and the progression of diabetes-related vascular complications [14]. PDGFR is another important actor in this topic, its levels are typically elevated in diabetes, promoting insulin resistance. This dysregulation also seems to correlate with low adiponectin levels, which increase following imatinib administration via differentiation induced in mesenchymal cells [13]. The role of other TKI targets, such as EGFR, is less clear, but they could represent an important target for the glycemic balance of treated individuals [15].

Based on this evidence, it has been proposed that TKIs could offer a novel therapeutic approach for diabetes. This led to a clinical trial evaluating imatinib for the treatment of patients with newly diagnosed type 1 diabetes mellitus, which showed promising results during the first 12 months. However, these benefits were not sustained at the 24-month follow-up. Additionally, some typical TKI-related adverse effects were observed and must be taken into account. Currently, no TKIs have received approval specifically for diabetes treatment [16].

It is important to underline that, on one hand, it is evident that some TKIs, such as Imatinib, Gefitinib, Dasatinib, Axitinib, and Sunitinib [12] have a positive effect on glycemic control in patients, while, on the other hand, drugs like Nilotinib have shown a detrimental effect on glycemic profiles [17]. To date, only hyperglycemia has been reported in patients with Non-Small Cell Lung Cancer (NSCLC) treated with EGFR TKIs targeting T790M [18]. Of the 28 oncological TKIs currently approved by the FDA/EMA hyperglycemia has been associated to Alectinib, Axitinib, Ceritinib, Dabrafenib and Trametinib [19–23].

The situation becomes even more complex when considering multikinase inhibitors, newer-generation drugs that are currently widely used. Studies on these inhibitors, such as Lenvatinib, Vandetanib, and Cabozantinib, are not consistent regarding their effect on glycemic profiles. A recent review suggests that the effect of these drugs on mean glucose levels may be slightly unfavorable (without leading to severe hypoglycemia or hyperglycemia), although data across studies are mixed [24,25]. Notably, Sorafenib in multikinase inihibitors group has shown clearly hyperglycemic effects in various studies, but has also been associated with hypoglycemia in some clinical trials [26,27]. Table 1 summarizes the different effects on blood glucose caused by various molecules belonging to the TKI class.

Although several other mechanisms may also play a role, studies on novel anticancer agents targeting IGF-1R, IR, or the PI3K/AKT/mTOR pathways have improved our understanding of at least one major mechanism—namely, the inhibition of IGF-1R/IR and/or PI3K/AKT/mTOR—as a key contributor to TKI-induced hyperglycaemia [28]. Sunitinib mainly targets VEGFR2 but has much weaker effects on IGF-1R and the insulin receptor (IR) and for this reason it has been associated with severe hypoglycemia in several cases [29,30]. Elevated insulin and C-peptide levels during hypoglycaemia suggest that sunitinib may cause excessive insulin production and tapering the drug often leads to gradual improvement. On the other hand, hyperglycemia was described in 15% of RCC patients treated with sunitinib [31]. Vandetanib strongly inhibits VEGFR2 and EGFR, with minimal activity on IGF-1R and IR. Although the mechanism is unclear, it may cause hypoglycemia through effects similar to those of sunitinib.

Table 1. Effect of major TKIs on blood glucose.

	Receptor Target	Applications	Hypoglycemic Effect	Hyperglycemic Effect	Neutral/ Unknow Effect	Reference
Imatinib	BCR-ABL	Ph + Acute LL CEL, GIST, MPM/MDS, DFSP, HES	X			[4,32–34]
Gefitinib	EGFR/ERBB	NSCLC	X			[4,15]
Dasatinb	BCR-ABL, SRC	Ph + Acute LL, CML	X			[4,6]
Axitinib	VEGFR	RCC	X (poor data available)			[4,35]
Sunitinib	PDGFR /VEGFR/c-KIT	HES, GIST MPM/MDS	X			[4,35]
Nilotinib	BCR-ABL	Ph+ Acute LL		X		[4,17,36]
Rociletinib	EGFR	NSCLC		X		[18]

Table 1. *Cont.*

	Receptor Target	Applications	Hypoglycemic Effect	Hyperglycemic Effect	Neutral/ Unknow Effect	Reference
Lenvatinib	PDGF/VEGFR/FGFR/RET/KIT	DTC			X	[4,24,25]
Vandetanib	VEGFR/EGFR/RET	MTC			X	[4,24,25]
Cabozantinib	MET//VEGFR	HCC, MTC, RCC			X	[4,24,25]
Sorafenib	PGFR /VEGFR/KIT/RET	RCC, HCC, DTC	Some episode of hypoglycemia reported	X		[4,26,27]
Selpercatinib	RET	NSCLC RET fusion, MTC-RET mutant, DTC RET fusion			X	[4]

Abbreviations: BCR-ABL: Breakpoint Cluster Region-Abelson, Ph+ :Philadelphia chromosome, LL: Lymphocytic leukemia, CEL: Chronic Eosinophilic Leukemia, GIST: Gastrointestinal Stromal Tumors, MPN/MDS: Myeloproliferative/Myelodysplastic Syndromes, DFSP: Dermatofibrosarcoma Protuberans, HES: Hyper eosinophilic syndrome, EGFR/ERBB: Epidermal Growth Factor Receptor/Erythroblastic oncogene B, NSCLC: Non-Small Cell Lung Cancer, SRC: proto-oncogene tyrosine-protein kinase Src, CML: cronic myeloid leukemia, VEGFR: vascular endothelial growth factor receptor, RCC: renal cell carcinoma, PDGFR: Platelet derived growth factor receptor, FGFR fibroblast growth factor receptor, RET: Rearranged during transfection, DTC: Differentiated Thyroid Carcinoma, MTC: medullary thyroid carcinoma, MET: Mesenchymal-Epithelial Transition factor, HCC: Hepatocellular Carcinoma.

3.2. Management

Due to the unpredictable effects of TKIs on blood glucose levels, close monitoring of glucose homeostasis is essential. This should include regular HbA1c testing and self-monitoring of blood glucose. Additionally, patients should be educated to recognize the symptoms of both hypoglycemia and hyperglycemia.

There are currently no official guidelines for the management of TKIs-induced hyperglycemia. Villadolid et al. [37] proposed an initial management strategy for hyperglycemia associated with EGFR-TKIs targeting the T790M mutation (Figure 1). They recommended general treatment goals such as: (1) fasting plasma glucose (FPG) < 160 mg/dL, (2) random plasma glucose < 200 mg/dL, and (3) glycate hemoglobin (HbA1c) ≤ 8%. They also suggested that less stringent glycemic targets might be appropriate for patients with advanced cancer, due to the risk of hypoglycemia.

Given the underlying mechanism—primarily insulin resistance—the preferred treatment for anticancer drug-induced hyperglycemia involves the use of insulin-sensitizing agents. Among these, metformin is considered the first-line therapy in most cases, due to its proven efficacy, safety profile, affordability, and extensive clinical experience. In clinical trials of rociletinib [18] 40–50% of patients across dose cohorts reported the use of at least one glucose-lowering agent effective against insulin resistance, most commonly metformin (used by 32–42% of patients).

TKI-induced hyperglycemia, which might otherwise necessitate dose reduction or discontinuation of a clinically effective TKI, justifies the therapeutic use of metformin. Moreover, it presents a potential opportunity to enhance the anticancer efficacy and clinical outcomes of TKI therapies. Current evidence suggests that metformin not only helps control TKI-induced hyperglycemia but may also, due to its intrinsic anticancer properties, improve the efficacy and safety of these treatments. It is important to note, however, that most of the available evidence supporting these benefits comes from preclinical or observational studies. There remains a pressing need for prospective randomized controlled trials (RCTs).

Peng et al. [38] recently explored the potential anticancer synergy between TKIs and metformin by studying the combination of gefitinib and metformin in bladder cancer. This combination demonstrated strong anti-proliferative effects, as well as inducing apoptosis in bladder cancer cell lines. Gefitinib inhibited EGFR signaling and reduced phosphorylation of ERK and AKT, while metformin enhanced these effects and boosted AMPK pathway activation.

On the other hand, the fact that some tyrosine kinase inhibitors can improve metabolic control in treated patients represents an undeniable benefit for the patient's overall health. This advantage may, in part, offset the disadvantages related to the increased cardiovascular risk often associated with TKI treatment (e.g., hypertension, etc.). It should also be considered that the direct effect of TKIs on diabetes may, in part, be modulated by indirect effects, as these drugs often cause adverse effects such as weight loss, diarrhea, nausea, or stomatitis [4].

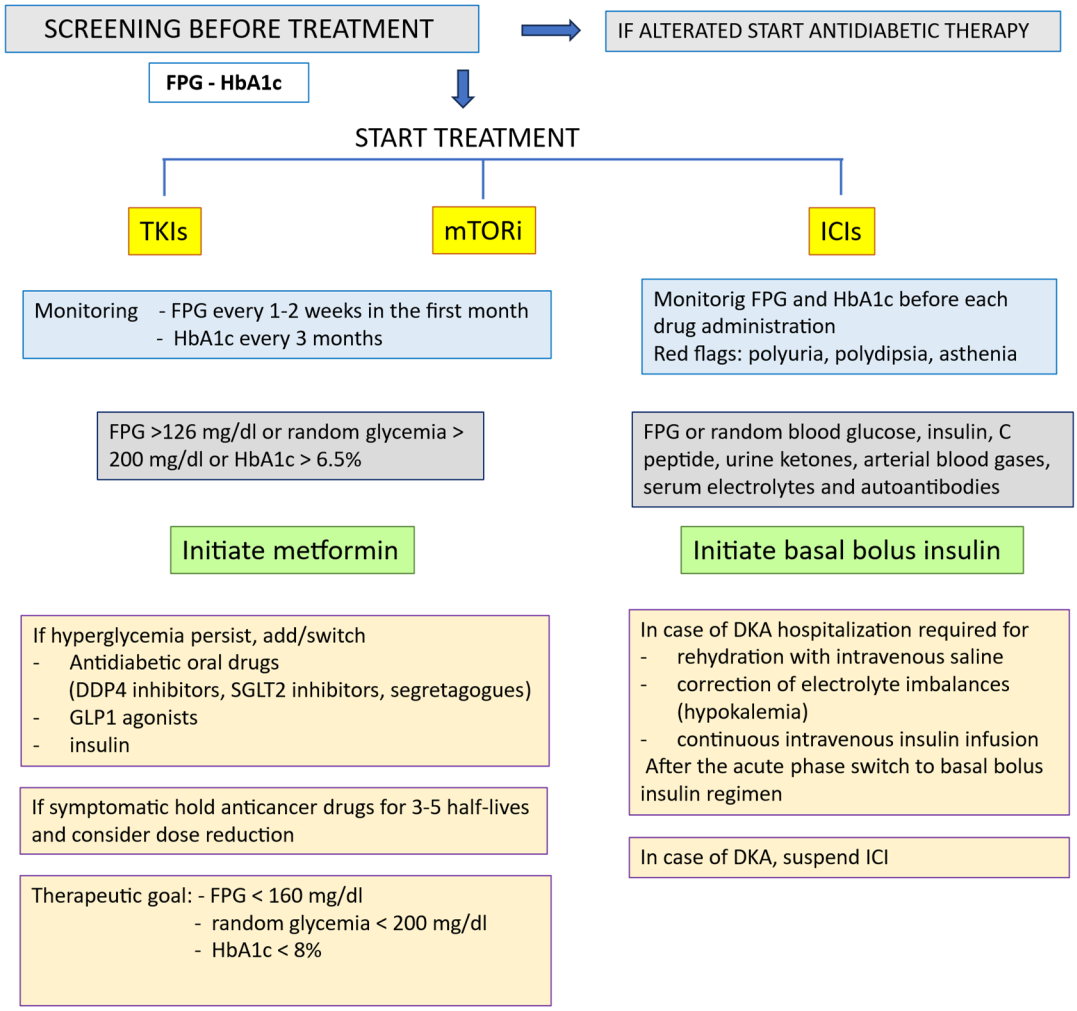

Figure 1. Management of diabetes mellitus induced by new oncological therapies. Abbreviations: FPG: Fasting Plasma Glucose; HbA1c: glycate hemoglobin; TKIs: Tirosin Kinase Inhibitors; mTORi: mTOR Inhibitors; ICIs: Immune Checkpoint Inhibitors; DDP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Co-Transporter 2; GLP-1: Glucagon-Like Peptide-1; DKA: diabetic ketoacidosis.

4. mTOR Inhibitors (mTORi)

Mammalian target of rapamycin (mTOR) inhibitors are anticancer therapies approved for the treatment of several malignancies. Only two mTOR inhibitors, everolimus and temsirolimus, have been approved by FDA in oncology field, in particular everolimus is approved for advanced renal cell carcinoma (RCC) [39], advanced progressive pancreatic neuroendocrine tumors (P-NETs) [40], advanced hormone receptor- positive breast cancer in combination with exemestane [41] and for subependymal giant cell astrocytoma associated with tuberous sclerosis [42] while temsirolimus is approved for RCC [43] and mantle cell lymphoma [44]. mTOR is a serine/threonine kinase, belonging to PI3K-related kinase family, involved in controlling growth, metabolism, and cancer development. mTOR forms two main complexes: mTORC1 and mTORC2. mTORC1 regulate cell growth, protein synthesis, inhibiting autophagy, and stimulating metabolism, it controls lipid metabolism by activating SREBP-1c, which induces lipogenic enzymes and promotes adipogenesis through PPARγ and lipin 1, supporting triglyceride synthesis. mTORC1-driven lipogenesis supports cancer progression by providing lipids for membrane synthesis. mTORC2 is less well understood, is activated by growth factors, and regulates Akt, SGK1, and PKC-α, affecting cell survival and cytoskeletal organization, it also may also regulate sphingolipid synthesis [45].

4.1. Effect on Glucose Metabolism

mTORC1 plays a complex role in glucose homeostasis. It promotes insulin resistance in adipose tissue by inhibiting insulin signaling through S6K1-mediated IRS1 phosphorylation [46]. Additionally, mTORC1 positively regulates pancreatic β-cell mass and function, enhancing insulin secretion and glucose control [47]. The role of the mTOR pathway and its inhibition by mTOR inhibitors is complex and sometimes contradictory.

mTOR inhibitors exhibit a 'Janus effect' on glucose metabolism, where both too much and too little mTORC1 activity can harm metabolic homeostasis. Short-term rapamycin treatment impairs glucose metabolism, while prolonged treatment improves insulin sensitivity and lipid profiles [48]. Moreover, rapamycin can worsen glucose homeostasis by impairing insulin secretion and causing insulin resistance, partly through disruption of mTORC2 [14]. Similar effects are seen with other mTOR inhibitors. In summary, although mTOR inhibition can enhance insulin sensitivity acutely, chronic inhibition disrupts insulin signaling through mTORC2 suppression, leading to peripheral insulin resistance. Additionally, impaired mTORC2 function in β-cells compromises insulin secretion. The net clinical effect of prolonged mTOR inhibition is thus hyperglycemia due to combined insulin resistance and β-cell dysfunction.

Impaired glucose regulation is a common complication in patients treated with mTOR inhibitors like everolimus. Hyperglycemia is one of the main side effects but occurs less often when everolimus is used as an immunosuppressant compared to cancer treatment, likely due to the lower doses used. Interestingly, the highest rates of diabetes were found in patients with advanced RCC rather than in those with P-NET, which are theoretically more likely to cause diabetes. In P-NET studies the incidence of all-grade hyperglycemia ranged from 12% to 25% with a major grade 3 or 4 ranged from 5% to 18% [40,49]. Phase II and III studies in patient with RCC treated with everolimus showed a higher incidence of hyperglycemia at any grade (range 50–58%) than in patient with P-NET, whereas grade 3 and 4 were similar [39,50] In phase II studied of patients with urothelial cancer, gastric cancer and sarcoma the incidence of hyperglycemia ranged from 66% to 93% [51–53].

However, many studies did not report whether patients were taking glucose-lowering medications or their dosages, and patients with uncontrolled diabetes were generally excluded, which may affect the data.

In a meta-analysis including 24 trials for a total of 4261 patients treated with temsirolimus, everolimus and ridaforolimus for solid tumors, the incidence rate of hyperglycemia of all grade was 0.25 (95% CI, 0.17–0.33) and of grade 3–4 was 0.07 (95% CI, 0.05–0.09). The incidence rate ratio (IRR) of all grade hyperglycemia was 2.95 (95% CI, 2.14–4.05) and of grade 3–4 hyperglycemia was 5.25 (95% CI, 3.07–9.00) [54]. Another meta-analysis including 3879 patients with various tumors treated only with everolimus, reported an incidence of all grade hyperglycemia of 6.8% and a high-grade hyperglycemia of 2.5% with a significant highest incidence in renal cell carcinoma (27.2%) and the lowest in breast cancer [55].

4.2. Management

A Task Force of the US National Cancer Institute Investigational Drug Steering Committee and a French expert committee proposed a specific management of mTOR-induced hyperglycemia [56] (Figure 1).

Before initiating treatment with an mTOR inhibitor, it is advisable to assess both FPG and HbA1c in all patients. After starting therapy, FPG should be monitored every two weeks during the first month, then monthly, while HbA1c should be measured every three months. In individuals with pre-existing diabetes, blood glucose self-monitoring should be intensified.

If FPG exceeds 126 mg/dL (7.0 mmol/L), random plasma glucose exceeds 200 mg/dL or if HbA1c is greater than 6.5%, treatment with metformin is recommended—provided there is no renal failure—as it is the first-line therapy for insulin resistance induced by mTOR inhibitors. If hyperglycemia is not adequately controlled with metformin alone, additional oral antidiabetic agents, such as sulfonylureas or Dipeptidyl Peptidase-4 (DPP-4) inhibitors, should be added. In some cases, injectable therapies like Glucagon-Like Peptide-1 (GLP-1) receptor agonists or insulin might also be considered. The recommended HbA1c target is between 7 and 8% and ketonuria should be measured when glycemia > 250 mg/dl in order to exclude diabetic ketoacidosis. Ongoing metabolic monitoring is recommended following discontinuation of mTOR inhibitors, as diabetes may remit in a substantial subset of patients, potentially requiring reassessment and adjustment of antidiabetic therapy [57].

Some authors demonstrated also a potential synergic effect of everolimus and metformin use in diabetic patients with pancreatic neuroendocrine tumors: PFS was significantly longer in patients with diabetes treated with metformin than in patients with diabetes receiving other antidiabetic treatments [58], but this positive effect of metformin on PFS has not been confirmed by another study [59].

Bono et al. [60] analyzed outcomes in metastatic RCC patients with everolimus-induced hyperglycemia from two large studies (RECORD-1 and REACT). Patients with hyperglycemia had higher response rates (82% vs. 69% in RECORD-1; 68% vs. 54% in REACT) and longer median progression-free survival (7.3 vs. 4.5 months in RECORD-1). Treatment duration was also longer for those with hyperglycemia. These differences suggest clinically relevant benefits. Notably, 18% (RECORD-1) and 31% (REACT) of hyperglycemic patients were on metformin, raising the possibility that metformin contributed to better outcomes. Further analysis based on metformin use is needed.

5. Immune Checkpoint Inhibitors (ICIs)

ICIs are monoclonal antibodies targeting immunoregulatory pathways, which physiologically inhibit immunological responses to prevent autoimmune mechanisms during pathogenic infections. The idea of using these agents for cancer treatment stems from studies on the tumor microenvironment and the mechanisms of immune evasion. It has been shown that cancer cells can induce an alteration of the expression of key molecules involved in immune regulation. By avoiding recognition by the host's immune defenses, tumor cells gain a survival advantage that promotes accelerated metastatic progression [61]. Among the targeted immune checkpoints, the first to be therapeutically exploited was CTLA-4, a receptor expressed on T lymphocytes that counteracts their activation by competing with CD28 for binding to CD80 and CD86, thereby inhibiting T cell costimulation. In 2010, the FDA approved the use of Ipilimumab, the first anti-CTLA-4 monoclonal antibody, for the treatment of metastatic melanoma.

Another receptor that has garnered significant research interest is PD-1, which is also expressed on T cells but more widely distributed than CTLA-4. PD-1 regulates immune response suppression through its interaction with PD-L1 and PD-L2. Following preclinical and clinical studies, the FDA approved Pembrolizumab in 2014 as the first anti-PD-1 monoclonal antibody for the treatment of metastatic melanoma, followed shortly thereafter by Nivolumab [62,63]. This new class of anticancer agents has also demonstrated efficacy in other tumor types, including renal cell carcinoma, non-small-cell lung cancer, Hodgkin lymphoma, urothelial carcinoma, and colorectal cancer, resulting in improved overall survival and increasing their use in clinical practice. As a result, clinicians must be equipped to promptly identify and manage the associated adverse events [64].

5.1. Immune Related Adverse Events and ICI-Related Diabetes Mellitus (ICI-DM)

In addition to inhibiting tumor immune escape, ICIs also interfere with physiological mechanisms of immune tolerance, thereby promoting the development of autoimmune processes that can involve multiple organ systems. Among the most frequent manifestations are myocarditis, colitis, arthritis, and dermatological reactions such as maculopapular rashes, pruritus, and hypopigmentation. The endocrine immune-related Adverse Events (irAEs) associated with ICIs include thyroid dysfunctions, both hypothyroidism and hyperthyroidism, which are more commonly observed with Nivolumab and Pembrolizumab. Conversely, hypophysitis is predominantly associated with Ipilimumab. Less frequently, other irAEs include adrenal insufficiency and the onset of diabetes [65–67].

ICI-DM is still the subject of ongoing studies and is predominantly described in case reports, often presenting with variable clinical features. However, understanding its clinical features and management remains crucial, given the frequent need for insulin therapy in these patients, who are already vulnerable due to their underlying malignancy.

The incidence of diabetes mellitus appears to be related to the type of ICI administered and the use of combination therapies. Evidence suggests that the onset of diabetes occurs in approximately 1% of patients treated with PD-1 inhibitors. Conversely, the incidence of ICI-DM seems to be lower with Ipilimumab; in fact, some retrospective studies do not appear to show a significant association [68–70]. Unlike classic type 1 diabetes mellitus (T1DM), ICI-DM occurs more frequently in older male patients and may appear as early as one week after starting therapy. Its incidence also appears to be influenced by ethnicity and, similar to T1DM, it is more commonly reported in Scandinavian countries (particularly Finland) and in Sardinia. (36.5/100,000 per year) [71].

5.2. Pathogenic Mechanisms

ICI-DM should be considered a form of autoimmune type 1A diabetes, given both the presence of autoantibodies commonly found in classic type 1 diabetes and the involvement of reactive T cells responsible for pancreatic beta-cell destruction. The underlying pathogenesis involves a loss of immune tolerance and the development of autoreactive T lymphocytes, resulting in T cell-mediated destruction. This is thought to result from the cytotoxic activity of autoreactive CD8+ T cells, supported by CD4+ Th1 cell. Further supporting this mechanism, immunohistochemical analyses performed on the pancreas of a patient treated with combined Nivolumab and Ipilimumab therapy revealed both widespread intrapancreatic T cell infiltration and reduced PD-L1 expression in the remaining beta cells, which appeared more severely damaged than those typically observed in classic type 1 diabetes. Moreover, evidence from NOD mouse models has shown that the PD-1/PD-L1 signaling pathway plays a key role in regulating immune responses, as blocking or eliminating PD-L1 accelerates the onset of diabetes [72–75]. As in autoimmune T1DM, beta-cell destruction leads to the release of intracellular proteins, such as the enzyme glutamic acid decarboxylase (GAD). For this reason, the presence of autoantibodies typically associated with T1DM is often observed. The prevalence of autoantibody positivity, however, appears to be variable. Some studies have reported a higher incidence of anti-GAD antibodies (around 50%), while the presence of islet cell antibodies (ICA) (13%), islet antigen-2 (IA-2) (18%), and zinc-transporter 8 (ZnT8) (4%) antibodies

are less frequent. Moreover, the presence of autoantibodies seems to be associated with a shorter interval between the initiation of immune checkpoint inhibitor therapy and the onset of diabetes, which in these cases tends to present more frequently as diabetic ketoacidosis (DKA) [76–79]. Genetic predisposition, as observed in other autoimmune diseases, appears to play a role in the pathogenesis of ICI-DM. In fact, predisposing HLA haplotypes commonly associated with T1DM, and fulminant diabetes have been identified, including respectively DR4-DQ8, DR3-DQ2 and DR9-DQ9, DR4-DQ4 [77]. Therefore, the presence of a predisposing haplotype is associated with an increased risk of developing other ICI-related endocrinopathies. In conclusion, the pathogenesis of ICI-DM shares several features with autoimmune diabetes, including the involvement of genetic, environmental, and immunological factors in the destruction of pancreatic beta cells [71].

5.3. Laboratory and Clinical Features

In patients receiving ICIs, diabetes most often presents with DKA, typically accompanied by symptoms such as polyuria, polydipsia, and marked asthenia, frequently requiring hospitalization. In some cases, severe dehydration caused by hyperosmolarity may lead to acute pre-renal failure. This makes it essential for clinicians to promptly recognize these symptoms, especially considering that these individuals are typically elderly oncology patients, in whom the development of such a complication significantly increases both morbidity and mortality risk. Blood glucose levels are usually markedly elevated, with mean values around 600 mg/dL, and, as in classic autoimmune diabetes, there is either absent or inadequately suppressed C-peptide, reflecting rapid and severe pancreatic β-cell exhaustion. Some patients also exhibit laboratory evidence of pancreatic inflammation, with elevated amylase and lipase levels. As previously described, several studies have highlighted important similarities with type 1 autoimmune diabetes, particularly regarding the appearance of diabetes-related autoantibodies, which may further worsen the clinical course [80–82]. Nonetheless, T1 DM and ICI-DM are not entirely identical. Increasing evidence suggests that it may represent a distinct clinical entity, separate from classic autoimmune diabetes. Notably, unlike T1D, ICI-DM often lacks the characteristic “honeymoon phase”, a transient period of partial β-cell function recovery, likely due to the rapid and profound destruction of β-cells, as indicated by the early disappearance of C-peptide levels at diagnosis. Additionally, it is important to emphasize that cases of ICI-DM without detectable autoantibodies have also been documented, further supporting the notion of a unique pathogenic mechanism [83]. From a clinical and biochemical perspective, ICI-DM typically presents in two distinct forms. On one hand, particularly in cases with detectable autoantibodies, the disease manifests as fulminant diabetes, a rapid-onset form, characterized by severe hyperglycemia accompanied by only modestly elevated HbA1c levels, reflecting an abrupt and early loss of pancreatic β-cell function. In a recent retrospective study [84] involving 76 patients diagnosed with ICI-DM, 68% presented with DKA. Notably, all patients exhibited pancreatic atrophy, with a significant median pancreatic volume reduction of 41% as assessed by computed tomography.

On the other hand, a more insidious form has been described, with a delayed onset, higher HbA1c levels at diagnosis, and a more gradual progression of hyperglycemia, suggesting a certain degree of latency in disease development. Interestingly, these latter cases often appear to be associated with protective HLA haplotypes against diabetes, further underscoring the heterogeneity of ICI-DM and its distinction from classical autoimmune diabetes [85]. In patients with pre-existing type 1 diabetes, immunotherapy has been shown to act as a trigger for the development of diabetic ketoacidosis. Conversely, in those with pre-existing type 2 diabetes, a worsening of glycemic control has been observed in some cases during treatment [86].

5.4. Management

Consistent with its underlying pathogenesis, ICI-DM presents as an insulin-dependent diabetes; therefore, management should follow the same principles as for type 1 diabetes. In cases of DKA, hospitalization is required due to the severity of the condition. In hospital setting, management includes rehydration with intravenous saline, correction of electrolyte imbalances (as hypokalemia) and continuous intravenous insulin infusion. Immunotherapy with ICIs should be suspended until the resolution of ketoacidosis. Outside of the acute phase, it is appropriate to initiate a subcutaneous basal-bolus insulin regimen, to be adjusted according to glycemic trends. (Figure 1). Given the potential occurrence of such an adverse event, it is essential for oncologists to monitor for hyperglycemia during treatment and promptly involve endocrinologists when necessary. If clinical suspicion arises for insulinopenic diabetes, insulin therapy should be initiated as early as possible to prevent complications [87–90]. To optimally manage this adverse event and reduce the risk of DKA, it has been proposed to monitor blood glucose and glycated hemoglobin levels prior to initiating ICI therapy and before each subsequent administration. Patients should be informed about the potential onset of hyperglycemia-related symptoms and, in high-risk cases (pre-existing autoimmune diseases or other endocrine irAEs), advised to perform regular self-monitoring of blood

glucose. At the time of diabetes diagnosis, it is recommended to assess diabetes-related autoantibodies, C-peptide, insulin levels, serum electrolytes, acid-base balance, and urine ketones to enable immediate initiation of appropriate treatment. Although ICI-induced diabetes is a rare complication, when it occurs it can progress rapidly to a life-threatening condition. Early recognition is therefore crucial to avoid interruptions in oncologic therapy and to improve patient outcomes [90,91]. Recent evidence and expert consensus suggest that, in patients who develop ICI-DM, continuation of immunotherapy may be acceptable in cases of mild hyperglycemia. However, when severe hyperglycemia or DK occurs, ICI therapy should be withheld until metabolic control is achieved and toxicity has improved to grade 1 or lower. Once glycemic stability is maintained under insulin replacement therapy, resumption of ICI treatment may be cautiously considered in a multidisciplinary setting, ideally involving both endocrinology and oncology specialists [71,92]

6. Other Therapies and Their Effect on Glucose Metabolism

6.1. AKT and PI3 Inhibitors

AKT and PI3K inhibitors are targeted therapies that interfere with the PI3K/AKT signaling pathway, a key regulator of cell growth, proliferation, and glucose metabolism. By inhibiting this pathway, these drugs can induce hyperglycemia, primarily through insulin resistance and reduced peripheral glucose uptake. The main approved agents are Alpelisib and Capivasertib.

Alpelisib is a selective PI3Kα inhibitor, approved for HR+/HER2-advanced or metastatic breast cancer with PIK3CA mutations. Hyperglycemia is common and can be severe, requiring frequent glucose monitoring and initiation of metformin or other antihyperglycemic agents [93].

Capivasertib, an oral pan-AKT inhibitor targeting the PI3K/AKT/mTOR pathway, mainly used in hormone receptor-positive, HER2-negative advanced breast cancer, can impair insulin signaling and glucose uptake, leading to hyperglycemia in approximately 15–17% of treated patients, with severe cases (Grade 3–4) occurring in 2–3%. Hyperglycemia typically emerges early during therapy, particularly in patients with pre-existing metabolic risk factors. Management primarily involves metformin as first-line therapy, with insulin reserved for severe or refractory cases. SGLT2 inhibitors should be used cautiously due to the risk of euglycemic ketoacidosis. Importantly, hyperglycemia induced by capivasertib is generally reversible upon dose reduction or discontinuation, though ongoing glucose monitoring is recommended for high-risk patients [94,95].

6.2. Enfortumab

Enfortumab Vedotin is an antibody-drug conjugate (ADC) targeting Nectin-4, a protein highly expressed on urothelial carcinoma cells actually approved for the treatment of locally advanced or metastatic urothelial carcinoma in patients previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitors. Although hyperglycemia is not among the most common adverse effects, recent data indicate a measurable risk, with any-grade hyperglycemia reported in approximately 10.3% of patients and grade ≥ 3 hyperglycemia in 5.7% Even patients without pre-existing diabetes can develop significant hyperglycemia or diabetic ketoacidosis (DKA), and therefore blood glucose monitoring during treatment is recommended, especially in patients with elevated BMI or baseline HbA1c [96].

7. Conclusions

Diabetes mellitus is a common adverse event associated with novel antineoplastic therapies. In patients with pre-existing diabetes, it is crucial to optimize glycemic control prior to the initiation of oncologic treatments. Furthermore, regular monitoring of blood glucose levels and HbA1c is recommended throughout the course of therapy.

TKIs can exert both positive and negative effects on blood glucose levels; hyperglycemia, driven by insulin resistance, benefits from the use of metformin. A similar mechanism is observed with mTOR inhibitors, for which the same treatment is recommended. In contrast, a different pathogenic mechanism underlies ICI-induced diabetes mellitus, which resembles type 1 diabetes mellitus; therefore, insulin therapy is indicated in these cases. Special vigilance is required for patients with ICI-DM, as the condition frequently presents initially with DKA, a life-threatening endocrine emergency that necessitates prompt recognition and management in an intensive care setting. Other drugs, although less common, can also cause hyperglycemia: AKT/PI3 kinase inhibitors and Enfortumab Vedotin can all induce hyperglycemia through insulin resistance or impaired insulin secretion. Management includes regular glucose monitoring, lifestyle measures, and use of metformin or insulin when needed.

The management of hyperglycemia as an adverse effect of anticancer therapies is crucial for oncologists and often requires interdisciplinary collaboration with endocrinologists to ensure optimal outcomes for affected patients.

Author Contributions

Conceptualization M.A. and M.M.; methodology: M.M. and M.A.; data curation: M.M., V.S. and E.C., writing—original draft preparation, M.M., V.S. and E.C.; writing—review and editing, M.B., R.L. and G.P.; supervision M.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

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