REVIEW

Novel cancer therapies and their association with diabetes

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Abstract

Over the last decade, there has been a shift in the focus of cancer therapy from conventional cytotoxic drugs to therapies more specifically directed to cancer cells. These novel therapies include immunotherapy, targeted therapy and precision medicine, each developed in great part with a goal of limiting collateral destruction of normal tissues, while enhancing tumor destruction. Although this approach is sound in theory, even new, specific therapies have some undesirable, 'off target effects', in great part due to molecular pathways shared by neoplastic and normal cells. One such undesirable effect is hyperglycemia, which results from either the loss of immune tolerance and autoimmune destruction of pancreatic β-cells or dysregulation of the insulin signaling pathway resulting in insulin resistance. These distinct pathogenic mechanisms lead to clinical presentations similar to type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. Both types of diabetes have been reported in patients across clinical trials, and data on the mechanism(s) for developing hyperglycemia, prevalence, prognosis and effect on cancer mortality is still emerging. With the rapidly expanding list of clinical indications for new cancer therapies, it is essential to understand the impact of their adverse effects. In this review, we focus on hyperglycemia and diabetes related to cancer therapies, describe what is known about mechanism(s) leading to dysregulated glucose metabolism and provide a guide to management of complex oncology patients with a new diagnosis of diabetes.

Introduction

Over the last decade, the field of oncology has seen the emergence of new therapeutic modalities such as immunotherapy, targeted therapy and precision medicine (Simpson *et al.* 2016). These approaches have become a mainstay of cancer therapy because of better tolerability, improved efficacy and less toxicity compared to conventional cancer treatments (Simpson *et al.* 2016, Au

et al. 2017). Broadly, the concept behind immunotherapy is to engage the immune system to destroy cancer cells. For example, the now widely used immune check point inhibitors (ICPI) loosen T-cell tolerance by blocking key regulatory proteins that are critical for 'self-identification'. By removing the breaks on the immune system, cancer cells that have breached immune surveillance are targeted

and destroyed (Salvatore *et al.* 2013). However, this mechanism can also lead to unwanted immune actions and a number of autoimmune endocrinopathies have been described with immunologic modulation including T1DM (Hughes *et al.* 2015, Barroso-Sousa *et al.* 2018). Although T1DM is a rare complication of ICPI, there is an interest in understanding the autoimmune mechanism, as well as concern about the management and long-term prognosis for patients who develop this side effect (Jonathan *et al.* 2017). These concerns are amplified by the success of these agents in treating cancer and their expanding use. Following the introduction of the first agent, ipilimumab in 2011 for metastatic melanoma, multiple agents targeting other key immune targets like the programmed cell death/ligand (PD1/PDL1) axis have entered the market (Culver *et al.* 2011). In the last 7 years, nivolumab, pembrolizumab, durvalumab, atezolizumab and tremelimumab have become available and their clinical applications are expanding rapidly to include metastatic melanoma, non-small-cell lung cancer, renal cell carcinoma, bladder carcinoma, head and neck cancer and lymphomas (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm, accessed 3/17/18).

Unlike immunotherapy, targeted cancer therapy is directed at specific molecular pathways involved in carcinogenesis, including regulation of cell growth, apoptosis and cancer progression (Pérez-Herrero & Fernández-Medarde 2015). While theoretically specific and effective, in practice there is some overlap of the targets of these signaling pathways in cancer cells and normal cells raising the potential for adverse effects including hyperglycemia. For example, the insulin signaling pathway is a key pathway utilized by cancer cells to promote cellular proliferation, growth and angiogenesis. Thus, some new drugs that target the insulin signaling pathway carry a risk for causing insulin resistance, impaired insulin secretion or both and have been associated with the development of both T1DM and T2DM (Yang & Yee 2012).

It is important to note that a concurrent diagnosis of diabetes is associated with increased risk of all-cause mortality in patients with cancer. A large body of evidence suggests that women with diabetes who develop breast, colon, pancreatic, liver or endometrial cancer have a higher all-cause mortality (El-Seraq *et al.* 2006). Furthermore, in men the risk for all-cause mortality is increased in patients diagnosed with diabetes and colon, liver or pancreatic cancer (Campbell *et al.* 2012). These associations suggest an adverse impact of diabetes on cancer survival. However,

the impact of new-onset diabetes from these novel cancer therapies on preexisting cancer is still unknown due to the lack of long-term safety and mortality data. In this review, we aim to provide readers with a summary of currently available information regarding cancer therapies and their association with diabetes. Special attention will be given to novel drugs and their effects.

Cancer therapies that reduce insulin secretion

Immune check-point inhibitors (ICPI)

Immune checkpoint inhibitors (ICPI) are immunotherapy agents that work primarily by using the immune system to target and eradicate cancer cells. Currently, ICPI include three drug classes of monoclonal antibodies named after their targets: anti-cytotoxic T-lymphocyte 4-antigen antibody (anti-CTLA-4 Ab), programmed cell death-1 inhibitors (PD-1 inhibitors) and programmed cell death ligand-1 inhibitors (PDL-1 inhibitors) (Diesendruck & Benhar 2017). Examples of drugs in these categories are ipilimumab and tremelimumab (anti-CTLA-4 Ab), nivolumab and pembrolizumab (PD-1 inhibitors), atezolizumab and durvalumab (PDL-1 inhibitors) (Ryder *et al.* 2014, Robert *et al.* 2015; Table 1). The first drug approved by the USA Food and Drug Association (FDA) in this category was anti-CTLA-4 inhibitor ipilimumab, based on observations that it increased disease-free survival from a median of 6.4–10.1 months in metastatic melanoma patients (Hodi *et al.* 2010). Additional drugs in the category of ICPI have entered the market in less than a decade and were projected to expand from a total market share of 1 billion dollars in 2013 to 7 billion dollars by 2020 (Webster 2014).

ICPI have undesired off-target effects, collectively referred to as immune-related adverse events (irAE). Overall, irAE are seen in approximately 50–60% of patients treated with ICPI, with some of the most commonly reported morbidity caused by autoimmune colitis and hepatitis (29–32% and 6–8% of treated patients respectively), dermatitis (43–45% of treated patients), and less commonly endocrinopathies (6–8% of treated patients) (Byun *et al.* 2017). However, with their growing use in clinical practice, emerging data from observational studies and clinical trials suggest that endocrinopathies may be more common than previously reported (Barroso-Sousa *et al.* 2018).

Endocrinopathies reported in clinical trials include lymphocytic hypophysitis (0–17%), Grave's disease

Table 1 Cancer therapies that reduce insulin secretion.

Drug category	Drug name	Drug target	Clinical indications	Type of diabetes	Mechanism of development of hyperglycemia	Reported incidence of hyperglycemia
Immune check point inhibitors	**CTLA-4 inhibitors:** Ipilimumab Tremelimumab	CTLA-4 receptor	Metastatic melanoma	T1DM	Autoimmune destruction of beta cells	0.02%
	PD-1 inhibitors: Nivolumab Pembrolizumab	PD-1 protein	1. Classic Hodgkin's lymphoma 2. Recurrent or metastatic head and neck squamous cell carcinoma 3. Renal cell carcinoma 4. Metastatic melanoma 5. Metastatic non-small cell lung cancer 6. Locally advanced or metastatic urothelial carcinoma 7. Hepatocellular carcinoma 8. Gastric or gastroesophageal junction adenocarcinoma 9. Metastatic colorectal cancer	T1DM	Autoimmune destruction of beta cells	0.02%
	PDL-1 Inhibitors: Durvalumab Azetolizumab	PD-L1 protein	1. Locally advanced or metastatic urothelial carcinoma	T1DM	Autoimmune destruction of beta cells	0.02%

and thyroiditis (6%–20%), less commonly reported primary adrenal insufficiency and type 1 diabetes (T1DM) (Wolchok *et al.* 2010). More recently, in a systematic review of ten randomized control trials where the relative risk of endocrinopathies observed with single agent ICPI was compared to placebo or control it was noted that the relative risk of all-grade hypothyroidism, hyperthyroidism, hypophysitis and adrenal insufficiency was 8.26 (95% CI: 4.67–14.62); 5.48 (95% CI: 1.33–22.53); 22.03 (95% CI: 8.52–56.94) and 3.87 (95% CI: 1.12–13.41) respectively (Abdel-Rahman *et al.* 2016). Although T1DM was reported in several of the clinical trials included in this systematic review, the data are sparse and were insufficient to estimate a relative risk (Abdel-Rahman *et al.* 2016, Barroso-Sousa *et al.* 2018).

Despite uncertain data on the true prevalence of T1DM among ICPI users, PD-1 inhibitors have been associated with rapid-onset hyperglycemia within days to weeks after the first dose nivolumab or pembrolizumab (Hughes *et al.* 2015). These patients also present with features and biochemical findings seen in T1DM. For example, patients who develop hyperglycemia following ICPI use

present with acute-onset hyperglycemia associated with life-threatening complications like diabetic ketoacidosis (DKA) that can be indistinguishable from new-onset T1DM (Hughes *et al.* 2015). In a case series of five hyperglycemic PD-1 inhibitor-treated patients, three of five patients had positive glutamic acid decarboxylase-65 antibodies (GAD-65 Ab). Most patients presented with DKA, undetectable C-peptide levels and positive GAD-65 Ab similar to classic T1DM (Hughes *et al.* 2015). At this time, there are limited data on reversal of T1DM with withdrawal of ICPI and reported patients remain treated with insulin (Hughes *et al.* 2015).

Mechanism for development of autoimmune diabetes

ICPI block immune inhibitory mechanisms, constricting the immunologic definition of self, and potentially allowing predisposition of autoimmunity to become unmasked. Specifically, two key inhibitory nodes, CTLA-4 and PD-1, are blocked, permitting distinct patterns of T-cell activation. Blockade of the CTLA-4 pathway causes general activation of the immune system and blockade of

PD-1/PDL-1 pathway allows cancer cells to be identified as non-self-antigens (Boutros *et al.* 2016).

CTLA-4 is cell-surface receptor expressed on the surface of the T-cells involved in the early activation of the immune system. Antigen-presenting cells (APC) present antigens (Ag) via the major histocompatibility complex (MHC) to the inactivated T-lymphocyte. T-lymphocytes have two key regulatory receptors, inhibitory CTLA-4 and activating CD28. When the receptor B7 located on the APC binds to CTLA-4 receptor, the T-cell is inactivated and when B7 binds to CD28 the T-cell gets activated. In order to activate the T-cell, B7 must bind to CD28. Ipilimumab (monoclonal antibody to CTLA-4 receptor) enables this by binding to the CTLA-4 receptor allowing the B7 ligand to freely engage with CD28 receptor activating the T-cells (Boutros *et al.* 2016; Fig. 1).

In contrast, blocking the PD-1 pathway allows the immune system to recognize and destroy cancer cells as non-self-antigens. PD-ligand is expressed on cancer cells which bind to the PD-1 receptors expressed on the surface of activated T-cells. This results in the deactivation of the T-cell allowing cancer cell survival. For cancer cells to be detected and destroyed, T-cells must identify them as non-self-antigens, which is made possible by the binding of PD-1 and PDL-1 monoclonal antibodies to these receptors. This allows for cancer cell detection (Boutros *et al.* 2016; Fig. 2).

Despite a general understanding of how ICPI modulates the immune system and targets cancer cells, the mechanism by which they cause autoimmune endocrinopathies, including what may be a version of T1DM, is not known. Some possibilities can be inferred from experimental data reported prior to the development of ICPI as anti-cancer drugs. In a study of autoimmune diabetes in non-obese diabetes (NOD) mice, it was noted that the majority of animals given PD-1 (76.5%) and PD-L1 (82.4%) inhibitors developed T1DM within a week compared to only 20% in non-treated littermates. Of note, CTLA-4 blockade in NOD mice did not affect the rate of diabetes onset compared to controls, supporting the clinical observation that T1DM is seen mostly in patients receiving PD-1 or PD-L1 inhibitors (Delovitch & Singh 1997, Ansari *et al.* 2003). Whether T1DM from these agents in humans follows the same phenomena as reported in NOD mice is an area under investigation.

At this time, there is consensus that ICPI raise the risk for autoimmune T1DM. However, the clinical course, biochemical markers, outcomes and long-term follow-up of such patients are areas of uncertainty and limited knowledge. In the future, as more data emerge,
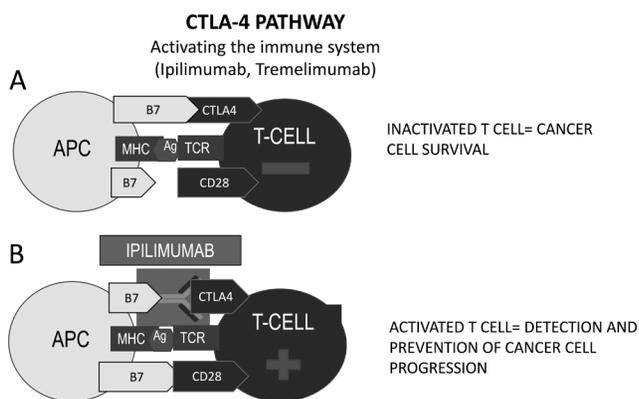

Figure 1

CTLA-4 is cell-surface receptor expressed on the surface of the T cells involved in the early activation of the immune system. Antigen-presenting cells (APC) present antigens (Ag) via the Major Histocompatibility Complex (MHC) to the inactivated T-lymphocyte. T-lymphocytes have two key regulatory receptors, inhibitory CTLA-4 and activating CD28. (A) Receptor B7 located on the APC binds to inactivating CTLA-4 receptor, and the T-cell is inactivated allowing cancer cell survival. (B) When ipilimumab (monoclonal antibody to CTLA-4 receptor) binds to the CTLA-4 receptor, T-cell activating B7 ligand freely engages with CD28 receptor activating the T-cells resulting in cancer cell destruction. Adapted/Translated by permission from Macmillan Publishers Ltd: Nature, Nature reviews clinical Oncology, Safety profiles of anti-CTLA-4 and anti-PD-1antibodies alone and in combination. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A *et al*. 2016.
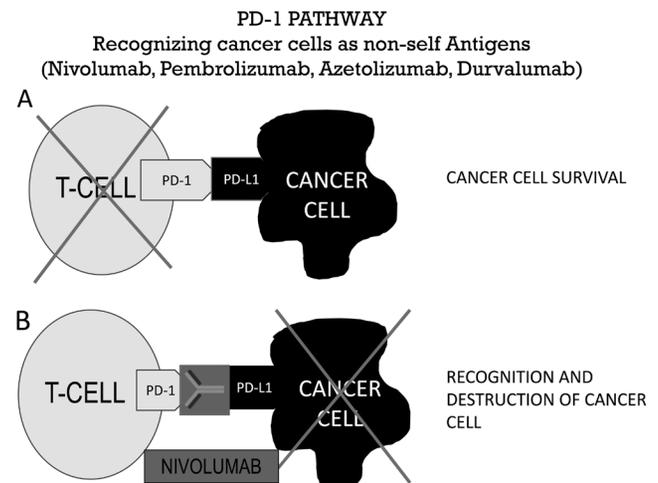

Figure 2

(A) T cells are deactivated when programmed cell death-1 receptor (PD-1) binds to the PD-L1 ligand expressed on the cancer cell surface, which allows cancer cell survival. (B) When PD-1/PDL-1 inhibitors bind to the PD-1 or PDL-1 receptors respectively, T-cell is able to recognize cancer cells resulting in cancer cell destruction. Adapted/Translated by permission from Macmillan Publishers Ltd: Nature, Nature reviews clinical Oncology, Safety profiles of anti-CTLA-4 and anti-PD-1antibodies alone and in combination. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A *et al*. 2016.

it may be possible to predict individual risk, identify these patients earlier and prevent ICPI-induced metabolic decompensation. Meanwhile, the acuity of development of T1DM in this focused high-risk population may offer deeper understanding into the molecular pathways and help identify therapeutic targets for treating T1DM in the future.

Somatostatin analogues and diabetes

Somatostatin analogues like octreotide, lanreotide and pasireotide in addition to being the mainstay of treatment for acromegaly have been used for the treatment of refractory neuroendocrine tumors both for symptom control and as a cancer therapy agent (Van Op den Bosch *et al.* 2009). Somatostatin has a dual effect on both insulin and glucagon mediated by somatostatin receptors, sstr2 and sstr5, which are expressed in the pancreatic islet cells (Hauge-Evans *et al.* 2009). Somatostatin inhibits insulin release by activating sstr2 and sstr5 receptors and inhibits the release of glucagon by the activation of sstr2 receptor (Singh *et al.* 2007). Hence, a variable effect of somatostatin analogues on glucose homeostasis has been noted due to their characteristic affinity toward each of these receptors. Pasireotide has a 39-fold higher affinity to bind with sstr5 and a lower affinity toward sstr2 (Bruns *et al.* 2002). During a 24-week prospective study to investigate the efficacy and safety of using pasireotide in the treatment of acromegaly, hyperglycemia was the most common adverse event and reported in 54 out of 61 patients enrolled (88.5%) and the mean HbA1c increased from 6.1 to 7.8% during week 12–24 of the study. In addition, at the end of 24 weeks, a baseline HbA1c of >5.7% was determined to be the most important predictor for development of diabetes. Most patients who did not have a prior diagnosis of diabetes in the study were successfully managed with oral agents and only 3 out of 46 (9.8%) required intensive management with insulin (Muhammad *et al.* 2018).

In contrast to this, hypoglycemia has been noted with octreotide due to its affinity toward suppressing glucagon production more than insulin production (Schmid & Schoeffer 2004). With the use of these agents it is important to recognize their functional affinity to different somatostatin receptors dictates whether a patient will develop hyperglycemia or hypoglycemia. In the future, long-term follow-up studies are required to determine if the patients exposed to these drugs and did not develop diabetes require frequent monitoring and early intervention.

Cancer therapies that induce insulin resistance

The effect of cancer therapy on insulin resistance (IR) is best appreciated by understanding the molecular pathways involved in the development of IR. Insulin is a polar polypeptide hormone that binds to its cell-surface insulin receptor, which has extracellular (α) and intracellular (β) domains. Binding of insulin to the α subunit initiates auto-phosphorylation and activation of the tyrosine kinase component of the β domain. The activated tyrosine kinase phosphorylates insulin receptor substrate 1 (IRS-1), which when triggered, activates phosphatidylinositide-1 kinase (PI 3-kinase) that generates phosphatidylinositol phosphate 2 and 3 (PIP-2 and PIP-3). PIP-3 phosphorylates the serine/threonine protein kinase Akt or protein kinase B (PKB), which has a broad range of actions including potentiation of membrane translocation of the glucose transporter GLUT4, which is required for insulin-mediated glucose transport across the cell membrane (Boucher *et al.* 2014).

From the perspective of cancer therapy, the insulin signaling pathway is of great interest since it is critical for cancer progression and hyperglycemia can be seen as a surrogate marker of successful blockade (Singh *et al.* 2014). In considering hyperglycemia as a common consequence of treatment with these agents, the established effect of diabetes on cancer mortality looms as a potentially important long-term consideration (Chang *et al.* 2004). Each of the therapies discussed below, target key elements of this pathway (Fig. 3 and Table 2).

Tyrosine kinase inhibitors (TKI) and their relation to diabetes

Tyrosine kinase activation of the intracellular β domain of the insulin receptor is a key first step in insulin signaling and more generally activates a family of enzymes involved in cell proliferation, growth, cellular metabolism and angiogenesis (Arora & Scholar 2005). Blocking these pathways is a key component for antiangiogenic therapies such as TKIs. Examples of these drugs include sorafenib, sunitinib, pazopanib, axitinib, vandetanib, lenvatinib, erlotinib, gefitinib and regorafenib which have been used to treat renal cell carcinoma, hepatocellular carcinoma, medullary thyroid cancer, pancreatic neuroendocrine tumors, gastrointestinal stromal tumor, adenosquamous cell carcinoma of the lung and small-cell lung cancer (Arora & Scholar 2005, Li & Lu 2018).
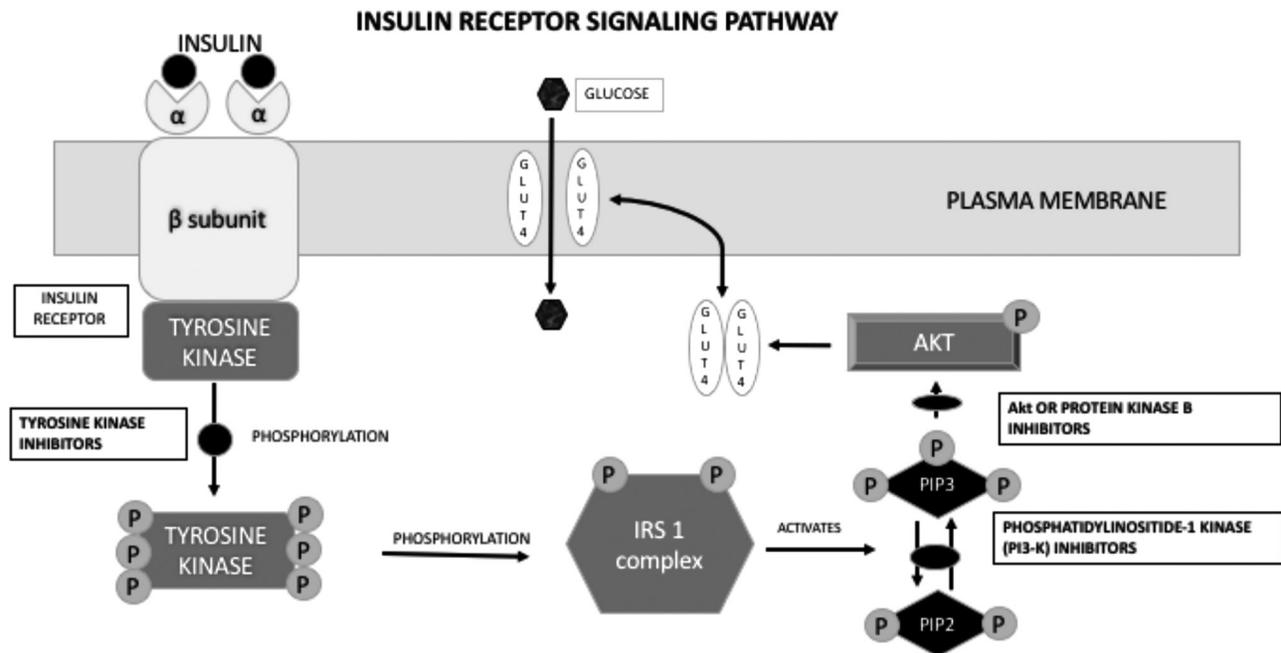
Figure 3

Insulin binds to its cell-surface insulin receptor, which has extracellular (α) and intracellular (β) domains. Binding of insulin to the α subunit initiates auto-phosphorylation and activation of the tyrosine kinase component of the β domain. The activated tyrosine kinase phosphorylates insulin receptor substrate 1 (IRS-1), which when triggered, activates phosphatidylinositide-1 kinase (PI 3-kinase) that generates phosphatidylinositol phosphate 2 and 3 (PIP-2 and PIP-3). PIP-3 phosphorylates the serine/threonine protein kinase Akt or protein kinase B (PKB), which have a broad range of actions including potentiation of membrane translocation of the glucose transporter GLUT4, which is required for insulin-mediated glucose transport across the cell membrane. Adapted/Translated by permission from Macmillan Publishers Ltd: Nature, Nature reviews clinical Oncology, Safety profiles of anti-CTLA-4 and anti-PD-1antibodies alone and in combination. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A *et al*. 2016. (doi: 10.1038/nrclinonc.2016.58. Epub 2016 May 4).

While blocking TK activity may cause insulin resistance, the overall effect of TKI in preclinical models is to reverse both T1 and T2 diabetes, and these agents are being considered in diabetes drug development (Hägerkvist *et al.* 2006, Louvet *et al.* 2008, Malek & Davis 2016). The mechanism of beneficial effects of TKI in diabetes is not fully understood, but in mice enhancement of beta cell mass was reported with the use of imatinib and sunitinib, a result that would be expected to compensate for IR (Hägerkvist *et al.* 2006). Additionally, mice pretreated with imatinib did not develop hyperglycemia after being exposed to the β-cell toxin streptozotocin suggesting a protective effect against beta cell apoptosis (Hägerkvist *et al.* 2006). In patients with preexisting diabetes receiving TKIs, mean blood glucose concentrations declined significantly with imatinib (−9 mg/dL), dasatinib (−53 mg/dL), sorafenib (−12 mg/dL) and sunitinib (−14 mg/dL) compared to normal controls. Remarkably, from this study 8 of the 17 patients with diabetes were able to discontinue their glucose-lowering medications, including insulin (Agostino *et al.* 2011). Hence, TKIs have been investigated as agents to treat and reverse T1DM

(Hägerkvist *et al.* 2006). While TKIs are being developed as a therapy for diabetes, these desirable off-target effects can be incorporated into management decisions for patients with preexisting diabetes.

Phosphatidylinositide-1 kinase (PI3-K) inhibitors and insulin resistance

PI3-K-protein kinase B (Akt)-mammalian target of rapamycin (mTOR) pathway is a key signaling pathway that regulates cellular proliferation, dehiscence and growth (Simioni *et al.* 2018). Mutations affecting the PI 3-Kinase pathway are present in many human cancer cells making it a target for therapeutics designed to inhibit cancer progression. In addition to being activated by insulin PI3-K is also activated by other growth regulators like epidermal growth factors, insulin-like growth factors and vascular endothelial growth factors making PI3K a key regulator of cell cycle checkpoints effecting apoptosis, proliferation and growth (Liu *et al.* 2009). However, blocking PI 3-kinase interferes with the normal process of insulin signaling that can result in insulin resistance. In 2014,

Table 2 Cancer therapies that induce insulin resistance.

Drug category	Drug name	Drug target	Clinical indications	Type of diabetes	Mechanism of development of hyperglycemia	Reported incidence of hyperglycemia
Tyrosine kinase inhibitors	Sorafenib Sunitinib Pazopanib Axitinib Vandetanib Lenvatinib Regorafenib	Block tyrosine protein Kinase activity	Renal cell carcinoma Hepatocellular carcinoma Medullary thyroid cancer Pancreatic neuroendocrine tumors Gastrointestinal stromal tumor Small cell lung cancer	Reverses T1DM and T2DM	Not known	Not known
Phosphatidylinosit IDE-1 kinase (PI3-K) inhibitors	Idelalisib Pilaralisib Copanisib	PI 3-Kinase pathway	Chronic lymphocytic lymphoma	T2DM	Blocking PI 3-kinase interferes with insulin signaling resulting in insulin resistance	28–30% reported incidence of hyperglycemia
Akt or protein kinase B inhibitors	GSK690693 MK2206	Akt/protein kinase B	Refractory or relapsed haematological malignancies Advanced breast cancer Ovarian cancer	T2DM	1. Reduces hepatic glycogen synthesis 2. Induces hepatic glycogenolysis 3. Blocking insulin signaling resulting in insulin resistance	Not known
Androgen deprivation therapy	Leuprolide Goserelin Triptorelin Histrelin	GNRH	Prostate cancer	T2DM	1. Hyperinsulinemia 2. Change in body fat composition	Not known

the FDA-approved idelalisib as the first PI3K inhibitor for use in chronic lymphocytic lymphoma (Yang *et al.* 2015). Even though idelalisib does not cause hyperglycemia, other drugs that target the same pathway, and currently being evaluated in clinical trials including pilaralisib and copanisib, have a 28–30% reported incidence of hyperglycemia (Nair & Cheson 2016). It is expected that the clinical application of these agents will expand due to their effects on key cancer signaling pathways, making it important to understand the epidemiology and clinical course of drug-induced diabetes. In particular, it will be important to know whether hyperglycemia induced by PI3K inhibitors is reversible or permanent after therapy is discontinued.

Protein kinase B (Akt) inhibitors and insulin resistance

Phosphoinositide-dependent serine threonine protein kinase (protein kinase B, Akt) is a key intermediary protein in the insulin signaling pathway especially in skeletal muscle and adipose tissue. Signaling through PI3-K/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) is also one of the fundamental pathways regulating cellular proliferation and growth (Simioni *et al.* 2018). Thus, it has been a very active area in cancer therapy development since PI3K/Akt pathway mutations are essential for cancer cell proliferation and progression (Crouthamel *et al.* 2009). Drugs designed to target this pathway cause insulin resistance and glucose intolerance as an expected on-target effect due to its direct influence on the insulin signaling pathway (Crouthamel *et al.* 2009). It has also been noted that Akt2-knockout mice have significant fasting hyperglycemia, post-prandial hyperglycemia and hyperinsulinemia compared to WT mice (Cho *et al.* 2001). Since AKt is involved in insulin-dependent glucose transport across the cell membrane, the effect on fasting and on post meal hyperglycemia was studied in mice treated with GSK690693, a pan-AKT kinase inhibitor. The findings showed significantly higher and prolonged hyperglycemia in non-fasted mice treated with GSK690693 compared to mice fasted for 16h prior to treatment with GSK690693. In addition, lower levels of hepatic glycogen (90% lower) was noted

in GSK690693-treated mice suggesting that Akt inhibition also reduced hepatic glycogen synthesis and induced hepatic glycogenolysis (Crouthamel *et al.* 2009). In the same study, the effect of common anti-hyperglycemics was evaluated in the mice treated with GSK690693. Pretreatment of mice with rosiglitazone for 7 days at a maximum dose of 5 mg/kg twice daily had no significant effect on the duration and severity of hyperglycemia. Furthermore, when insulin was added to rosiglitazone 30 min before starting treatment with GSK690693, there were only modest effects on the duration and severity of hyperglycemia. Based on these findings, it was suggested that Akt inhibitors cause hyperglycemia by a combination of mechanisms including insulin resistance, inhibition of glycogen synthesis and reduction of peripheral glucose uptake (Cho *et al.* 2001). GSK690693 and MK2206 are Akt inhibitors and are currently being investigated for treatment of refractory or relapsed hematological malignancies, advanced breast cancer and ovarian cancer. The results of these clinical trials are expected in the coming years and more data are needed to understand the effect and outcomes in humans especially due to the proposed multiple mechanisms of hyperglycemia noted in mice and the reported challenge providers face treating hyperglycemia with insulin and insulin sensitizers (https://clinicaltrials.gov/ct2/results?term=akt+inhibitors&Search=Search, accessed 3/22/18).

Androgen deprivation therapy and insulin resistance

Prostate cancer is one of the most commonly diagnosed cancers in men. The effectiveness of androgen deprivation therapy, either surgically with bilateral orchiectomy or medically with gonadotrophin-releasing hormone agonist (GnRH), has resulted in 5-year survival of 86% of patients with locally invasive or metastatic prostate cancer (Keating *et al.* 2006). In contrast to these desired effects on prostate cancer, GnRH agonists have deleterious effects on the body fat composition, increasing body weight and percentage fat body mass, while decreasing lean body mass and muscle size in men with non-metastatic prostate cancer, which causes increased IR (Smith *et al.* 2002). In addition, a separate study reported a near doubling of fasting insulin levels (6.89±4.84 mmol/L or 124±87.1 mg/dL to 11.34±8.16 mmol/L or 204.1±146.9 mg/dL) but a non-significant increase in fasting plasma glucose levels (5.6 mmol/L or 100.8 mg/dL to 6.0 mmol/L or 108 mg/dL) 3 months after androgen deprivation therapy was initiated with GnRH analogues (Dockery *et al.* 2003). Another observational study reported a higher risk of incident diabetes in patients treated with androgen deprivation therapy compared to non-treated patients and patients treated with bilateral orchiectomy (Keating *et al.* 2006). This further establishes the association of diabetes with androgen deprivation therapy.

In contrast to the increased incidence of several cancers in patients with diabetes, prostate cancer is an exception since men with diabetes have lower testosterone levels, which is considered protective against prostate cancer (Kasper & Giovannucci 2006). However, when the effects of hyperinsulinemia and increase fat mass from GnRH analogues is considered, the impact of this treatment is complex.

Cancer therapies that reduce insulin production and induce insulin resistance

Corticosteroids and diabetes

Corticosteroids (CST) are not novel to cancer therapeutics since drugs like prednisone, dexamethasone and methylprednisolone have been used to treat cancer, suppress inflammation, and the immune response in multiple malignancies for several decades (Bartlett *et al.* 2001). In addition to the direct effect on cancer progression, the benefit of improved tolerance to chemotherapy, treatment of associated nausea and appetite suppression has made potent, long-acting steroids one of the most commonly prescribed drug classes in the field of oncology (Hesketh 2008). In contrast to the benefits seen in cancer patients, the undesirable effect of CST on blood glucose control has been clearly established since steroids not only exacerbate preexisting diabetes, but also induce hyperglycemia and precipitate diabetes in patients with no known prior history of diabetes (Van Raalte *et al.* 2009). Based on a single-center experience, about 68% patients treated with greater than 40 mg or equivalent dose of prednisone daily for >2 days experienced hyperglycemia (Blood glucose >200 mg/dL) (Table 3). Among the patients who did not have a prior history of diabetes, 56% experienced at least one episode of hyperglycemia (Donihi *et al.* 2006). This indicates the high prevalence of hyperglycemia in the steroid-treated, cancer patients, which is often undertreated.

IR seen in steroid-induced diabetes follows a similar pattern to T2DM. About 60–80% patients treated with steroids, develop hyperglycemia, explained by specific targeted effects at the level of the muscle, adipose tissue and the liver, which are all key tissues for maintaining blood glucose homeostasis. In the normal fasting state,

Table 3 Cancer therapies that induce insulin resistance and reduce insulin secretion.

Drug category	Drug name	Drug target	Clinical indications	Type of diabetes	Mechanism of development of hyperglycemia	Reported incidence of hyperglycemia
Corticosteroids	Prednisone Prednisolone Methylprednisolone Dexamethasone	Glucocorticoid receptor	Adjuvant chemotherapy	T2DM	1. Insulin resistance in muscle, liver and adipose tissue 2. Increases gluconeogenesis 3. Increase in glucagon and epinephrine 4. Pancreatic beta cell apoptosis	60–80%
Mammalian target of rapamycin (mTOR) inhibitors	Rapamycin Sirolimus Everolimus Temsirolimus	mTOR complex 1 and 2	Advanced pancreatic neuroendocrine tumors Advanced renal cell carcinoma Mantle cell lymphoma Breast cancer	T2DM	1. Phosphorylation of the IRS-1 complex which blocks the PI3K pathway in the liver, adipose tissue and muscle promoting tissue insulin resistance 2. Reduces beta cell mass and proliferation	5.25% (meta-analysis) 50% (RECORD trial)

the liver produces glucose to maintain euglycemia. In a state of low insulin, gluconeogenesis and glycogenolysis provide glucose for oxidation primarily by neural tissues. Steroids accentuate this finely tuned system and increase endogenous glucose production by activating genes involved in gluconeogenesis and enhancing the release of gluconeogenic substrates such as alanine from skeletal muscle. Steroids also indirectly blunt the effect of insulin by enhancing the effect of counter-regulatory hormones like epinephrine and glucagon, which also contribute to increased hepatic insulin resistance (Ruzzin *et al.* 2005).

In the skeletal muscle, steroids inhibit the translocation of the GLUT4 glucose transporter resulting in insulin resistance. Here, insulin-dependent glucose transport into the cells is inhibited by 30–50% in the presence of CST. In addition, there is also a 70% reduction in glycogen synthesis in the muscle resulting in hyperglycemia. In adipose tissue, CST increases the breakdown of lipids by inducing lipolysis and raising local accumulation of non-sterified fatty acids, a mechanism that has been associated with greater increasing insulin resistance (Perez *et al.* 2014). Apart from these effects on the liver, muscle and adipose tissue, it is postulated that CST has an effect on insulin secretion by direct effect on pancreatic beta cell by induction of apoptosis (Ranta 2006).

From the above, it is clear that CST causes IR and, to some extent, insulin secretory defects resulting in hyperglycemia and since it is commonly prescribed in the oncology population it is important to identify early and provide expectant treatment with a regimen adjusted for the type, frequency and duration of CST being prescribed. Clear communication between oncologists and providers managing DM can abbreviate the duration and severity of hyperglycemia. While managing hyperglycemia secondary to steroids attention must be paid to whether there is a preexisting history of T2DM where higher levels of IR is expected.

Mammalian target of rapamycin (mTOR) inhibitors and diabetes

mTOR inhibitors are a group of drugs that inhibit the PI3K-Akt mammalian target of rapamycin (mTOR) pathway. mTOR inhibitors like rapamycin, sirolimus and everolimus have been in use as organ transplant anti-rejection therapy for several years now (Touzot *et al.* 2012). More recently additional benefits of these agents as a cancer therapy has been identified due the inhibitory effect on critical pathways in carcinogenesis. Everolimus and temsirolimus have been recently approved for

advanced neuroendocrine tumors except for functional midgut tumors with carcinoid syndrome, advanced renal cell carcinoma that fails treatment with first line agents, mantle cell lymphoma and breast cancer (Yao *et al.* 2011).

Two major clinical trials involving the use of everolimus have reported significantly higher rates of hyperglycemia (fasting blood glucose >126 mg/dL) including the RECORD 1 and the BOLERO trial. In the RECORD trial for advanced renal cell carcinoma patients, about 50% subjects reported hyperglycemia and 12% reported severe hyperglycemia compared to 1% in the placebo controlled group (Motzer *et al.* 2008). Similarly, during the BOLERO 1 trial for advanced HER2-positive breast cancer, everolimus-treated patients reported a higher incidence of hyperglycemia compared to placebo-treated patients (12% compared to 5%; Hurvitz *et al.* 2015). A meta-analysis of 24 clinical trials including 4261 patients showed an incidence rate ratio of any grade hyperglycemia (fasting blood glucose >126 mg/dL) as 2.95 (95% CI, 2.14, 4.05) and severe grade 3 and 4 hyperglycemia (random blood glucose above 251 mg/dL) as 5.25 (95% CI, 3.07, 9.00) further supporting this association (Sivendran *et al.* 2014; Table 3).

Mechanism of hyperglycemia from mTOR inhibitors: mTOR is a kinase belonging to a family of enzymes packaged into 2 complexes, mTOR complex 1 and 2 (mTORC 1 and mTORC 2) that have distinct functions. When activated the mTORC 1 pathway promotes protein synthesis, cellular growth and proliferation with inhibition of autophagy and the mTORC 2 pathway activation promotes cellular proliferation and cell survival making these important targets for cancer treatment. With regard to diabetes, mTOR plays an important role in balancing insulin resistance and pancreatic beta cell function. mTORC 1 in addition to the above mentioned role in cellular proliferation causes the phosphorylation of the IRS-1 complex, which blocks the PI3K pathway in the liver, adipose tissue and muscle-promoting tissue insulin resistance (Khamzina *et al.* 2005). In contrast to this, mTORC 1 activation increases beta cell mass and proliferation of beta cells (Rachdi *et al.* 2008). Hence overall, mTOR pathway activation is involved in maintaining a balance in energy metabolism. With the use of mTOR inhibitors this balance is disrupted. Theoretically, blocking mTORC 1 should reduce insulin resistance, but this is not the case since the ability to cause insulin resistance depends on the dose and duration of mTOR inhibitor use where too much or too little inhibition can cause insulin resistance (Houde *et al.* 2010, Fang *et al.* 2013).

As described previously, mTORC 1 is also involved in pancreatic beta cell proliferation and inhibiting this will inadvertently result in reduced beta cell mass and proliferation. A 33% reduction in glucose-dependent insulin secretion was observed following treatment with rapamycin. In addition, in animal models, treatment with rapamycin reduced beta cell mass by about 50% due to increased cellular apoptosis (Fraenkel *et al.* 2008). This aspect of mTOR inhibitors incited the use of these agents for the therapeutic purpose of treating insulinomas due to their 'desirable' effect of reducing beta cell mass (Kulke *et al.* 2009).

Due to this established association between mTOR inhibitors and hyperglycemia, it is now recommended to screen patients with a hemoglobin A1c and a fasting plasma glucose before initiation of mTOR inhibitors and to repeat plasma glucose every 2 weeks for a month and then monthly after until treatment continues. This has enabled early recognition and treatment of hyperglycemia in these patients. However, the same level of scrutiny is not performed for newer agents where hyperglycemia is poorly characterized.

Conclusion

Development of hyperglycemia and diabetes is associated with increased mortality in commonly encountered cancers. New advances in cancer therapy including immune check point inhibitors, TKI, PI3-K inhibitors and Akt inhibitors promise better oncologic outcomes, but it seems likely that metabolic side effects will be an important consequence that will require clinical attention and better mechanistic understanding. The data available from preclinical models and human studies with the new cancer therapies suggest that the general pathology of common forms of diabetes, namely insulin resistance and/or impaired insulin secretion, can be exacerbated by novel anti-cancer agents. This is not surprising considering that signaling pathways targeted by new cancer therapies are also central to cellular metabolism. The long-term consequences of developing diabetes secondary to these new anti-cancer agents are poorly understood because of limited epidemiology. Specifically, it will be important to know the permanence or reversibility drug-induced diabetes, the risk of common macro and microvascular diabetic complications they confer, and the ultimate impact on cancer prognosis. Overall, understanding the relationship between specific cancers, new cancer therapies and secondary diabetes is important to optimize patient care. Moreover, this understanding may lead to new insights into diabetes pathogenesis and applications that can be applied beyond the field of oncology.

Author contribution statement

Afreen I Shariff: manuscript idea, preparation of the manuscript and data collection. Sohail Syed: Preparation of the manuscript. Rebecca Shelby: manuscript review. Jeremy Force: manuscript review. Jeffrey Clarke: manuscript review. David D'Alessio: manuscript review. Leonor Corsino: manuscript idea, data collection and manuscript review.

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