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REVIEW

Current cancer therapies and their influence on glucose control

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Abstract

This review focuses on the development of hyperglycemia arising from widely used cancer therapies spanning four drug classes. These groups of medications were selected due to their significant association with new onset hyperglycemia, or of potentially severe clinical consequences when present. These classes include glucocorticoids that are frequently used in addition to chemotherapy treatments, and the antimetabolite class of 5-fluorouracil-related drugs. Both of these classes have been in use in cancer therapy since the 1950s. Also considered are the phosphatidyl inositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR)-inhibitors that provide cancer response advantages by disrupting cell growth, proliferation and survival signaling pathways, and have been in clinical use as early as 2007. The final class to be reviewed are the monoclonal antibodies selected to function as immune checkpoint inhibitors (ICIs). These were first used in 2011 for advanced melanoma and are rapidly becoming widely utilized in many solid tumors. For each drug class, the literature has been reviewed to answer relevant questions about these medications related specifically to the characteristics of the hyperglycemia that develops with use. The incidence of new glucose elevations in euglycemic individuals, as well as glycemic changes in those with established diabetes has been considered, as has the expected onset of hyperglycemia from their first use. This comparison emphasizes that some classes exhibit very immediate impacts on glucose levels, whereas other classes can have lengthy delays of up to 1 year. A comparison of the spectrum of severity of hyperglycemic consequences stresses that the appearance of diabetic ketoacidosis is rare for all classes except for the ICIs. There are distinct differences in the

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reversibility of glucose elevations after treatment is stopped, as the mTOR inhibitors and ICI classes have persistent hyperglycemia long term. These four highlighted drug categories differ in their underlying mechanisms driving hyperglycemia, with clinical presentations ranging from potent yet transient insulin resistant states [type 2 diabetes mellitus (T2DM) -like] to rare permanent insulin-deficient causes of hyperglycemia. Knowledge of the relative incidence of new onset hyperglycemia and the underlying causes are critical to appreciate how and when to best screen and treat patients taking any of these cancer drug therapies.

Key Words: Cancer therapy; Hyperglycemia; adverse drug effects; Immune checkpoint inhibitors; mTOR inhibitors; 5-fluorouracil analogs; Glucocorticoids; Diabetes mellitus

Core Tip: Immune checkpoint inhibitors (ICI) rarely cause hyperglycemia, but glucose monitoring from their initiation is critical as rapid diabetic ketoacidosis can develop from underlying immune-mediated pancreatic beta-cell destruction. Therapy with mammalian target of rapamycin (mTOR) inhibitors, 5-fluorouracil (5-FU)-analogs and glucocorticoids have higher rates of hyperglycemia early in therapy that is not generally severe, but needs to be recognized and treated to optimize patient outcomes. The hyperglycemia occurring from the 5-FU and ICI classes is not reversible. The diabetes from ICIs arises from an absolute insulin deficiency *vs* the partial deficiency from the 5-FU class. Glucocorticoids and mTOR inhibitors predominantly cause insulin resistance.

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INTRODUCTION

Cancer therapies have had profound impacts on increased life expectancy over the past few decades, however, it is widely known to have a multitude of unintended effects. Quality of life concerns such as hair loss, intractable nausea or visible surgical scars are widespread in individuals initiating their treatment cycles. Physicians initiating chemotherapy are also concerned about treatment side effects and routinely monitor for signs or symptoms of serious complications that may require urgent hospitalization, a change in treatment management or a pause in therapy to avoid a life-threatening event. Hyperglycemia is a common and potentially significant adverse effect arising from the use of several widely applied cancer therapeutic classes including immune checkpoint inhibitors (ICIs), phosphatidyl inositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) inhibitors, 5-fluorouracil (5-FU) analogs, and glucocorticoids[1-4]. The latest understanding of the characteristics of the hyperglycemia that is associated with the use of these drug classes is presented in order to raise awareness of the adverse effects these agents have on glucose control to enable its early recognition, trigger regular monitoring plus timely intervention, and to ultimately improve patient outcomes. Emphasized below is the current knowledge pertaining to these drug classes regarding the incidence, onset, reversibility and severity of hyperglycemia associated with their use in cancer therapy.

The significance of hyperglycemia on cancer therapy outcomes

Untreated hyperglycemia has been associated with a multitude of negative outcomes for cancer patients including longer hospital stays[5], worsened prognosis and decreased survival[6,7]. Glucose is a key substrate metabolized by cells to produce ATP and is a preferred energy supply; cancer cells are known to increase their glucose uptake, with the subsequent increase in energy reserves able to support further cellular proliferation[8]. Hyperglycemia has also been associated with a reduction in

cancer therapy effectiveness[9], an increased rate of infections and sepsis in those who may already have immunosuppression from their cancer treatments[10], and an increased length in hospital[11,12]. Hyperglycemia fosters a proinflammatory environment that enhances the production of cancer stimulating signals that promote cell proliferation, increase resistance to cell death and may also induce drug resistance to chemotherapy[11-16]. Clinically, hyperglycemia has been found to be an independent risk factor for earlier cancer recurrences, and higher mortality rates[17].

Glucose levels and clinical presentation define the severity of hyperglycemia

The research referenced below has graded both the severity of hyperglycemia and the degree of clinical symptoms as a means of comparing patient adverse events (AE) with drug use. Four grades of severity are defined that consider glucose levels, but also includes the severity of the clinical consequence such a diabetic ketoacidosis (DKA) or permanent diabetes. Grade 1 AE (G1) relates to asymptomatic or mild symptoms, no ketosis or evidence of type 1 diabetes (T1DM), fasting glucose (FG) above normal. Grade 2 AE (G2) involves moderate symptoms, FG > 8.9-14 mmol/L, or the presence of ketosis or T1DM at any glucose level. Grade 3-4 AE are severe symptoms, that are medically significant or life-threatening, differentiated from G2 and each other by the degree of glucose elevations with Grade 3 AE (G3) encompassing glucose levels between 13.9-27.8 mmol/L, and Grade 4 AE (G4) including glucose levels > 27.8 mmol/L[18].

IMMUNE CHECKPOINT INHIBITORS

Immune Checkpoint inhibitors target one of three T-cell ligands to promote antitumor activity

A relatively new class of chemotherapy agents that are recognized for their potential side effects on glucose control are the immunomodulators that target and inhibit immune checkpoints, resulting in an increase in T-cell mediated immune responses that benefit patient treatment responses[19]. These ICIs are monoclonal antibodies that bind and block (inhibit) immune cell-cell interactions that would normally suppress the immune response. The result is that there is an effective and durable increase in antitumour activity[20]. This class is very successful in the treatment of advanced melanoma including those with *BRAF* mutations[21], and have since been used successfully for treatment of additional advanced stage cancers including hepatocellular carcinoma[22,23], non-small-cell lung cancer[24], renal cell carcinoma[25] and metastatic clear cell renal cancer[26]. The ICIs in current use specifically block three T-cell checkpoints; the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor, the programmed cell death-1 (PD-1) receptor, and the third and most recent class of antibodies targeting the programmed cell death-Ligand 1 (PD-L1)[19,20].

ICIs trigger immune-related endocrinopathies, and the incidence of diabetes with ICI differs with the checkpoint being targeted

There is an association between the use of these ICIs and the frequent appearance of immune-related AE, including a wide-spectrum of endocrine dysfunctions. The onset of hyperglycemia in individuals taking ICIs is infrequent, and the incidence differs depending on the receptor being targeted, as well as whether receptor targeting combinations are used[27]. Not all ICIs appear to have the same potential. The highest probability appears to reside in those targeting either the PD-1 receptor (nivolumab, pembrolizumab) or PD-L1 (atezolizumab, durvalumab, avelumab), whereas the CTLA-4 targeting agent (ipililmumab) does not seem to have a significant risk when used alone, as only a handful of case reports were noted[28]. A recent 2020 meta-analysis estimated the incidence of serious (G3 and G4) and all-grade hyperglycemia (G1-G4) in every reported case of ICI-associated diabetes, noting that the PD-1/PD-L1 targeted therapies were associated with hyperglycemia in 0.2%-4.9%, with a 0.49% incidence of serious hyperglycemia in patients using these drugs[1]. A 2018 study reported an overall incidence of 0.9%[28]. The combination of PD-1/PD-L1 and CTLA-4 immune-targeted therapy showed the highest overall rates of diabetes, spanning 2.0%-3.4% in different cohorts studies, and a notably higher rate of serious hyperglycemia events at almost 2%[28]. This same study confirmed that the CTLA-4 inhibitors do not seem to have a risk of hyperglycemia when used without PD-1 therapies[28].

ICI therapy stimulates immune-mediated antitumor activities, but also stimulates autoimmune disorders

The inhibitory monoclonal antibodies used to interrupt immune response checkpoints results in a reinvigoration of the immune response. The ICI antibodies bind and block the specific inhibitory ligand on the T-cell surface, interrupting those activity-dampening signaling pathways[29,30]. The result is T-cell activation and stimulation of their immune surveillance and antitumor activity, to the benefit of the patient[31]. However, immune checkpoints are also central to maintaining immunological self-tolerance and preventing autoimmune disorders[32,33]. Immune-mediated self-damage causing endocrine dysfunctions are one of the most common side effects of the ICI class, including loss of thyroid, adrenal and pituitary activity, plus rare cases of pancreatic insulin deficiency[34]. Autoimmune recognition and destruction of pancreatic beta (β)-cells is the well-established mechanism resulting in classic T1DM [35,36], and the ICI drugs likely trigger this same destructive loss of function in cancer patients who developed hyperglycemia[37]. Human pancreatic islets lack CTLA-4 receptors, but do present PD-L1 to protect them against immune cells[38]. The ICI monoclonal antibodies that bind PD-1/PD-L1 should be capable of inhibiting this pathway in pancreatic β-cells, leaving them susceptible to (auto)immune destruction and diabetes, providing a rationale why PD-1/PD-L1 but not CTLA-4 inhibitors are associated with new onset diabetes.

The hyperglycemia associated with ICI use is due to autoimmune destruction of the pancreatic ß-cells and loss of endogenous insulin release

With ICI use, the new onset of hyperglycemia found in those without diabetes, and the worsening glucose control in those with known diabetes, does appear to be directly due to immune-mediated pancreatic damage. Pancreatitis was found in 42% of individuals developing diabetes, and auto-antibodies classically associated with T1DM can be found elevated in these individuals, with 47% having glutamate decarboxylase autoantibodies[28]. The appearance of new hyperglycemia in those exposed to ICI therapy is not caused by an associated insulin resistance, as three large case series evaluating patients that developed diabetes after ICI exposure found low C-peptide (62%-93%), positive ketosis (59%-77%) and detectable autoantibodies (39%-56%)[28,37,39], with the antibodies in at least some cases not present prior to ICI treatment[28].

Loss of glucose regulation in type 2 patients taking ICIs may indicate a transformation into an insulin-deficient state

It is less well known how ICI use has impacted glucose levels in those with underlying T2DM as the stress of illness, pain, or other medical therapies may also contribute to loss of tight glucose control. It is well documented, however, that when blood glucose levels become acutely and significantly more difficult to control in known T2DM, that it is important to consider that the ICI therapy may have caused pancreatic β-cell dysfunction and insulin deficient diabetes[40].

The onset of Insulin-deficient diabetes after ICI therapy is unpredictable and is permanent

Of the cases of insulin-deficient diabetes (IDD) reported with ICI therapy, the onset is unpredictable and can appear as early as a few weeks after starting treatment, up to greater than one-year following therapy; over half occurred within 4 mo of treatment initiation, typically in their fourth cycle of therapy[28]. The presence of hyperglycemia with ICI therapy does not require cessation of the ICIs or provision of high dose steroid pulse therapy, as this does not appear to restore pancreatic function[41,42]. In fact, reversal of IDD after ICI use has rarely been reported. A single case of ICI-induced diabetes successfully used infliximab, an immunosuppressant, to reverse the hyperglycemia[43], yet in general, once present the hyperglycemia is persistent and does not appear to be mitigated by decreasing or stopping the ICI treatment[34,44].

ICI associated hyperglycemia has a high risk of serious and severe consequences, notably DKA and permanent diabetes

ICI therapy can lead to severe complications of hyperglycemia that can occur very rapidly. The severity is due to the damage to the pancreatic β-cells, leading to irreversible insulin deficiency. Because of this T1DM-like defect, there is a distinct risk of DKA, and this can be an acute and potentially life-threatening presentation. The association between ICI-dependent onset of hyperglycemia and ketosis/DKA was

remarkably high, at 77.8 % in newly diagnosed cases of diabetes[37]. There are many case reports of rapid DKA as the first presentation of hyperglycemia with ICI use, raising the possibility that this overlaps with Fulminant T1DM, a clinical presentation that is characterized by rapid development of markedly elevated glucose, near-normal glycated hemoglobin A1c (A1C), ketoacidosis, negative autoantibodies, severe insulin deficiency and elevated levels of pancreatic enzymes[45]. A careful review, however, revealed that there does appear to be distinct differences, including the presence of autoantibodies in ICI IDD, that are typically not found in Fulminant T1DM[37]. Due to the risk of DKA with this drug class, the practice guidelines developed to monitor for adverse effects of ICIs commonly recommend routine monitoring of glucose levels both at baseline, with each treatment cycle throughout induction and then every 3-6 wk thereafter for up to one year[18]. For safety, the use of insulin for diabetes developing from ICI therapy is recommended unless insulin deficiency can be ruled out[18].

PI3K/AKT/MTOR PATHWAY INHIBITORS

Inhibition of the PI3K/AKT/mTOR pathway interrupts multiple cancer promoting cell signals

The PI3K-AKT-mTOR signaling pathway plays a vital role in responding to nutrient abundance[46], making it an attractive target for blockade[47]. The proteins being inhibited are kinases that target downstream proteins for phosphorylation to change cellular responses including promoting normal cell growth and proliferation when nutrients are abundant[48]. They ultimately work within the same pathway as growth factors and insulin signaling, and can therefore also influence glucose and lipid metabolism[49].

mTOR, PI3K inhibitors and their derivatives are effective in many cancer types

mTOR inhibitors are derived from the original drug of this family, rapamycin, that was initially isolated as an antifungal agent[50], but was later determined to inhibit a kinase important in cancer growth[51]. This target was subsequently named "mechanistic target of rapamycin" or mTOR. mTOR inhibitors and their related analogs are used in many advanced stage solid tumors including renal cell, neuroendocrine tumors of the pancreas, and breast cancer[52]. There are presently three mTOR inhibitors approved by the United States Food and Drug Administration (FDA) that are derivatives of rapamycin; sirolimus, temsirolimus, and everolimus. Closely related medications are the PI3K inhibitors, of which there are four currently approved by the FDA; copanlisib, idelalisib, duvelisib, and alpelisib. These latter agents are approved for use in the treatment of breast cancer and hematological malignancies. AKT inhibitors and combination PI3K/mTOR inhibitors are still under development and some have entered Phase II clinical trials[53].

The hyperglycemia arising from the inhibition of mTOR is primarily due to insulin resistance

The usual activity of mTOR not only influences cell growth and development, but also affects glucose regulation[54]. mTOR inhibitors primarily promote hyperglycemia through increased insulin resistance *via* mTOR complex 1 (mTORC1) inhibition, as they impair the efficiency of the insulin signaling pathway at multiple points in its phosphorylation cascade[55,56]. In a diabetic rodent model, exposure to rapamycin resulted in a reduction in insulin signaling *via* proteins IRS1/2, a reduction in phosphorylation by AKT, and inhibition of PI3K activity[55]. Moreover, rapamycin increased the activation of Jun N-terminal kinase pathway, which is a pathway implicated in insulin resistance[55]. Together, the effect observed with these chemotherapy drugs is consistent with a predominant T2DM-like insulin resistant state, due to impaired insulin signaling[55]. Lastly, a component of insulin deficiency is also thought to play a role in the development of hyperglycemia as mTORC1 is a known positive regulator of pancreatic β-cell function, and molecular studies using pancreatic β-cells exposed to rapamycin detected a 33% reduction in glucose-induced insulin secretion[55].

There are two mTOR complexes that differ in their influence on glucose levels and sensitivity to inhibition

The mTOR complex is a serine/threonine protein kinase that exists in two different multi-protein complexes. The mTORC1 is sensitive to rapamycin, whereas complex 2 (mTORC2) is less responsive to rapamycin, although chronic exposure to rapamycin does ultimately result in reduced mTORC2 signaling[56]. The mTORC2 pathway is much less well characterized than the mTORC1 pathway. It was initially thought that the mTORC2 pathway was resistant to rapamycin treatment, but it was later discovered that long term exposure reduces mTORC2 signaling in some cell types by suppressing the assembly of the mTORC2 complex[57]. mTORC2 activates AKT, and the mTORC2-AKT pathway has been shown to promote pancreatic beta cell proliferation and survival, and to inhibit gluconeogenesis by blocking Fox01 activity[57]. Normal mTORC2-AKT activity also induces glucose uptake in insulin-sensitive tissues and blocks protein catabolism. The loss of mTORC2 activity through inhibition, therefore, increases insulin resistance as well as promoting protein catabolism and reducing muscle mass. Inhibition of mTORC2 also leads to the loss of the mTORC2-AKT-dependent inhibition of gluconeogenesis as well as decreased insulin production, contributing further to hyperglycemia[56]. The effect of mTORC1 and mTORC2 inhibition on glycemia is complex, and related to the degree and chronicity of inhibition, but ultimately treatment with all mTOR inhibitors leads to hyperglycemia [56]. The three mTOR inhibitors approved by the FDA are derivatives of rapamycin; sirolimus, temsirolimus, and everolimus, and are primarily mTORC1 inhibitors, although dual mTORC1/C2 inhibitors are in development[57].

The PI3K/AKT/mTOR pathway inhibitors are potent drivers of hyperglycemia

The incidence of hyperglycemia associated with the use of PI3K/AKT/mTOR inhibitors is significant and ranges between 12%-50%[2]. A 2015 meta-analysis considered twenty-four trials of mTOR inhibitor use in solid organ cancer treatment and noted a 5.25-fold increased risk of significant hyperglycemia (blood sugars > 14 mmol/L)[58]. Pre-existing diabetes was an independent risk factor for glucose levels > 14 mmol/L[59]. It is worth noting that the PI3K inhibitors can also induce hyperglycemia[60], and AKT inhibitors have revealed significant hyperglycemia in preclinical studies[61].

Most cases of hyperglycemia occur during initial exposure, are mild and transient

A retrospective study of 341 patients treated with PI3K and mTOR inhibitors revealed that the mean FG increased from 5.3 mmol/L at baseline to 7.1 mmol/L during the first chemotherapy cycle, but returned to 5.4 mmol/L prior to the next cycle[59]. This supports the conclusion that the rise in blood glucose is transient. The majority of these patients experienced their highest glucose levels early on in therapy, during the first (87.9%) or second (14.4%) cycle of mTOR inhibitor treatment, and most cases of hyperglycemia in this study were mild (G1)[59]. However, more significant glucose elevations can occur, as 6.7% of patients receiving this therapy had glucose elevations > 14 mmol/L compared to controls not taking mTOR inhibitors[62]. Additionally, it was observed that the median time of elevated glucose levels (> 8.3 mmol/L) was 56 d in patients showing clinical benefit, and 113 d for those patients who progressed[62]. It remains to be determined if the timing of new hyperglycemia development after therapy initiation is predictive of treatment responses.

mTOR-induced hyperglycemia is typically managed with oral therapies

Insulin deficiency or DKA are not significant risks with using this class of drugs, as only a very small percentage of patients require insulin[59]. and to our knowledge there have been no cases of hyperglycemic emergency or DKA in any clinical trials to date. A single case report was found that describes DKA and pancreatitis in a patient treated with everolimus for breast cancer, supporting that this is a very rare association with mTOR inhibitor drugs[63]. When uncontrolled hyperglycemia develops (defined as glucose > 14 mmol/L, A1C ≥ 9%), expert committee guidelines recommend stopping the chemotherapy medication and reintroducing it a lower dose in the rare cases of uncontrolled hyperglycemia despite optimal diabetes management [2]. Both American and French guidelines for PI3K/AKT/mTOR use are available to direct surveillance and treatment best practices[2,64], and an A1C target of ≤ 8% is suggested for pre-existing patients with diabetes prior to mTOR inhibition[2].

5-FU AND DERIVATIVES

5-FU is an antimetabolite agent that has been used in the initial treatment of breast, gastric, colon and pancreatic cancers and has been in active use for over sixty years[65,66]. It is a pyrimidine analogue that is structurally related to thymine, uracil and cytosine bases in DNA, RNA or both, respectively[67]. 5-FU acts as an antimetabolite to inhibit cell growth through its interference with DNA and RNA function upon its incorporation into newly synthesized DNA or RNA.

Derivatives of 5-FU have been created to increase their stability and to overcome their drug toxicities

Over the years, additional 5-FU oral prodrugs have been developed that reduce their toxicity and improve tumour selectivity, as well as increase their stability[68-70]. In the last 20 years, capecitabine has been developed and used predominantly for metastatic breast and gastrointestinal cancers[66,70]. It is activated into 5-FU through three sequential enzymes, with the final enzyme being found in high concentrations in tumour tissues[66]. As such, capecitabine activation is very targeted and is generally better tolerated[66,70]. There have been numerous reports of glucose disorders with 5-FU and its derivatives including case reports of hyperglycemia following the administration of the newest 5-FU prodrug, capecitabine[71].

5-FU prodrugs can contribute to new onset diabetes, and the majority have persistent hyperglycemia after therapy is stopped

There is a paucity of data on 5-FU therapies and their specific effects on glucose control. The majority of information comes from a 2013 study involving 362 patients with normal fasting plasma glucose prior to 5-FU-based therapies in which overt diabetes developed in 11.6% of individuals and impaired fasting glucose (IFG) in another 11.3%[3]. Of the 42 patients that developed diabetes, 32 occurred during therapy, with the remaining 10 being detected during follow-up after treatment was completed. Only 16% (7/42) of these patients had glucose levels spontaneously return to normal[3], indicating that the hyperglycemia related to 5-FU therapy is persistent in most cases. Those remaining were managed with a variety of interventions including diet (30%), insulin (10.8%) or oral medications[3]. Given that these patients did not have pre-existing risk factors for diabetes, it was thought that the development of diabetes was secondary to 5-FU chemotherapy[3].

Hyperglycemia typically develops early during 5-FU analog therapy, and is generally mild

The timing of new-onset hyperglycemia with 5-FU treatments varies, but most (77%) patients developed diabetes during their early chemotherapy cycles (median third cycle), and the remaining individuals present up to 1 year after completion of treatment[3]. It is unclear how 5-FU chemotherapy affects glucose control in those with established diabetes. In this study, the timing of the onset of IFG after 5-FU treatment was not reported[3]. While 5-FU-associated hyperglycemia was typically mild during active treatment (95% had glucose < 14 mmol/L), after therapy was complete it was noted that seven out of 42 patients developed significant hyperglycemia (>14 mmol/L), and one patient in the study died of ketoacidosis[3]. Aside from this study, there are two additional case reports of DKA associated with 5-FU based treatments [72,73].

5-FU therapies decrease pancreatic β-cell insulin storage and release

The underlying mechanism causing the hyperglycemia upon 5-FU exposure appears to be due to a decrease in insulin being released from the pancreatic β-cells[3,74]. Those patients who developed diabetes had a progressive decrease and delay in C-peptide secretion, seemingly due to a pancreatic deficiency in endogenous insulin processing and production[3]. A case control study also demonstrated that insulin levels failed to increase appropriately with the development of hyperglycemia[74]. Preclinical animal studies also suggest that hyperglycemia may result from impaired insulin production as there was a relative insulin deficiency in rats following 5-FU administration, as well as a decrease in the abundance of secretory granules in pancreatic islet cells[75]. Cellular studies designed to reveal how these drugs cause hyperglycemia have shown that 5-FU related therapy stimulates immune mediators in pancreatic β-cells, resulting in their destruction *via* cell-mediated T-cell infiltration[76]. Consistent with this, capecitabine has been linked to acute pancreatitis[77,78].

The rare cases of DKA reported with 5-FU therapies suggests that there is sufficient endogenous insulin production to offset severe hyperglycemia consequences in the majority of cases. Nonetheless, there is a real risk of significant glucose elevations, as 16.7% (7 of 42) of newly diabetic individuals had glucose levels > 14 mmol/L despite therapy[3]. Management of hyperglycemia following capecitabine therapy included successful treatment with dietary control and lifestyle changes[79,80], although some individuals did require insulin[3].

GLUCOCORTICOIDS

Glucocorticoids are a class of medications that have been used to treat a plethora of medical conditions since the 1950's. Glucocorticoids are prescribed widely for a variety of medical conditions, with estimates of use approaching 1% of the general population [81]. Although their efficacy and adverse effect profile have been described extensively in the literature, their effect on the human body varies due to the heterogeneous nature of the underlying disease states they are treating and the individuals who are using them; hence there is variability in their use and dosage recommendations[82].

Steroids are useful as adjunct therapy to offset adverse side effect of cancer treatments

Glucocorticoids are often included as a part of cancer therapy to mitigate the adverse effects of the chemotherapies being used at the same time. They can be very useful in controlling nausea and improving appetite, and are frequently given as an antiemetic before and after chemotherapy[83]. The dosing and duration often depends on the emetogenic potential of the chemotherapy. Glucocorticoids are also given to prevent some of the other adverse effects of chemotherapy like generalized rash or thrombophlebitis when drugs are given through peripheral vein, or to offset hypersensitivity reactions[11,84,85]. Glucocorticoids may also be included as an inherent part of the cancer therapy, such as their use within the CHOP protocol in lymphoma. There are several other regimens used in multiple myeloma and prostate cancer that include glucocorticoids as a part of the treatment, and the dosing and formulation varies.

Glucocorticoid-induced hyperglycemia is a very common adverse effect of steroid use

Along with their known benefits, there are many recognized adverse effects of glucocorticoids, both acute and chronic. Supraphysiologic glucocorticoid use is known to raise glucose levels, particularly at the high doses that are required for therapeutic advantages. Glucocorticoid-induced hyperglycemia (GIH) is a well-known complication of their use in individuals with known diabetes (T1DM and T2DM) as well as those who were previously euglycemic[4,86]. Hyperglycemia is commonly reported in patients undergoing cancer therapy that includes glucocorticoids, however its true incidence is hard to define due to the variability in chemotherapy combinations, durations, and cycles. One study of hospitalized patients taking high dose glucocorticoids reported hyperglycemia in 52% of patients[87], with another two studies reporting 34%[88] and 37%[89] in patients during induction therapy for acute lymphocytic leukemia[88,89]. A more recent study found that 94% of women with gynecological cancer whose chemotherapy regimen included high dose dexamethasone experienced hyperglycemia[85]. These patients were undergoing continuous glucose monitoring (CGM) which the authors felt led to the remarkably high incidence rate, and postulated that glucose elevations may be significantly under-recognized in many previous clinical trials that did not utilize CGM[85].

GIH occurs acutely and is generally mild

GIH is a phenomenon that typically occurs acutely with initiation[85,87,90,91], and hyperglycemia was found to be significant by day 2 in those being treated systemically for hematologic malignancies[11]. The degree of glucose elevations range widely and are most frequently modest (< 14 mmol/L)[92], nonetheless severe hyperglycemia (> 28 mmol/L) and DKA have also been reported[11,93], with rare reports of hyperglycemic hyperosmolar syndrome as well[94]. Other AE associated with GIH range from mild to serious, such as increased infections and lengthened of hospital stays[11,16,86,95-98]. The acute hyperglycemia associated with glucocorticoids will typically resolve upon discontinuation[4,99,100].

The formulation and duration of steroid use influences the incidence of hyperglycemia

The most commonly used glucocorticoids in chemotherapeutic regimens are prednisone (oral) and dexamethasone (oral or intravenous). The dose and duration at which they are used varies with the chemotherapy and clinical situation, making general conclusions difficult[16]. To give an example of the variance that confounds these clinical assessments, a study by Ochola *et al*[95] considered patient outcomes with prednisone use; there was a range in total daily doses of 40-150mg; once to four times daily; and between 5-14 d duration.

It is commonly considered that higher glucocorticoid doses and longer durations of use confers a greater risk of developing GIH[11,16,101,102], yet there have been exceptions to this association[82,94,98]. Most hospitalized patients developed hyperglycemia after taking ≥ 40 mg/d of prednisone for two days[103]. There is some evidence that splitting the dose of prednisone, rather than administering it all at once in the morning, may help reduce GIH[104]. The type of glucocorticoid used may also correlate with the risk of hyperglycemia[92]. Healy *et al*[11] found that hyperglycemia was associated with higher doses and the longer-acting steroids in those without diabetes, yet it was not in those with previous diabetes.

Due to the differences in the pharmacokinetic profiles of shorter acting glucocorticoids (such as prednisone, prednisolone, and hydrocortisone) *vs* longer-acting glucocorticoids such as dexamethasone, one could anticipate a delayed effect with the latter[90]. Prednisone levels peak 4-8 h after ingestion and its duration of action is between 12 h to 16 h; these pharmacokinetics correlated with increases in postprandial glucose in the afternoon and evening when administered in the morning[11,87,92]. During induction therapy for acute lymphoblastic leukemia the use of long-lasting dexamethasone was linked with a significant increase in risk of GIH when compared to those prescribed the intermediate-acting prednisone[93]. In contrast, a comparison between dexamethasone 8-12mg IV and prednisone 40mg orally found extensive hyperglycemia in the majority of all patients, without differences between the two therapies[94].

Steroids induce a potent insulin resistance resulting in hyperglycemia

The effects of glucocorticoids on glucose levels are complex[4]; although GIH occurs most commonly in patients with pre-existing diabetes, it also presents in those without any prior history of hyperglycemia[82,105]. Glucocorticoids can cause an increase in both fasting and postprandial glucose levels, but it is generally recognized that the largest impact is on postprandial levels[16,87,92,95,96,105,106]. High dose glucocorticoid use impairs insulin signaling, leading to key increases in insulin resistance at the liver (promoting hepatic gluconeogenesis) and skeletal muscle (impairing glucose uptake)[4,92,106]. Glucocorticoids can also diminish normal insulin secretion by pancreatic β-cells[4,99]. Some of the predictors of risk for increased blood glucose with glucocorticoid use in the context of cancer therapy include older age and higher BMI [88,98,102] and while an elevated A1C was found to be a predictor, a discrete HbA1c cut-off was not determined[85].

SUMMARY AND DISCUSSION

For all of these classes of drugs, it would be prudent to initiate glucose monitoring upon the initiation of chemotherapy and to continue to do so throughout treatment. As summarized in Table 1, glucocorticoids and AKT/mTOR inhibitors can be expected to cause the majority of patients (up to 94%[85] and 50%[2] respectively) to develop hyperglycemia very early after drug initiation. In contrast, the diabetes that develops upon the initiation of ICIs and 5-FU therapies will affect fewer individuals (up to 5%[1] and 11%[3], respectively) and could be anticipated to present at slightly later timelines on average, with the 5-FU analogs typically in their third chemotherapy cycle[3] and ICIs in their fourth chemotherapy cycle (about 4 mo[28]). Despite searching the literature, it was not found that there are dosing 'cut-offs' for any drug class below which the risk of hyperglycemia is nil, nor are there specified doses above which there are significantly increased rates of hyperglycemia.

The insulin resistance arising from either glucocorticoids or AKT/mTOR inhibitors nearly always resolved once the treatments have stopped[4,59,99,100] and there have not been any reports of delayed reappearance, implying that ongoing daily glucose monitoring will not be necessary upon completion (Table 2). When mild hyperglycemia is present, standard management approaches used for T2DM have been

Table 1 Summary of reported characteristics of hyperglycemia incidence, onset and severity with the use of current chemotherapy agents

Characteristics by drug class	Glucocorticoids	5-FU and analogs	PI3K/mTor inhibitors	Immune checkpoint inhibitors
Incidence of new or worsening hyperglycemia	Significant, 34%-94%	Common, 11.6% DM, 11.3% IFG	Significant, 12%-50%	Rare, 0.2%-4.9%
Onset of hyperglycemia after first use	Acutely	Majority by 3 mo; 3/4 early (3rd cycle); 1/4 up to 1 yr later	Majority after first use	Majority by 4 mo, can be after first use, can be up to 1 yr later
Severity of hyperglycemic events	Usually mild, Severe possible, Multiple reports of DKA and some HHS	Mild, Case reports of DKA	Mild, No DKA	Moderate to severe, 77.8% DKA

5-FU: 5-fluorouracil; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PI3K: Phosphatidyl inositol-3-kinase; mTOR: Mammalian target of rapamycin; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar syndrome; IFG: Impaired fasting glucose.

Table 2 Hyperglycemia can be a class or drug-specific effect and may not be reversible with discontinuation

Characteristics by drug class	Glucocorticoids	5-FU and analogs	PI3K/mTOR inhibitors	Immune checkpoint inhibitors
Class effect on hyperglycemia	Yes	Yes	Yes	Negligible risk with the CTLA-4 inhibitor, ipililmumab Does occur with all PD-1 and PD-L1 inhibitors, most significantly when combined
Reversibility of hyperglycemia	Yes	No	Yes	No

5-FU: 5-fluorouracil; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; PI3K: Phosphatidyl inositol-3-kinase; mTOR: Mammalian target of rapamycin; PD-1: Programmed cell death-1; PD-L1: Programmed cell death-Ligand 1.

effective including diet adjustments, oral metformin or sulfonylureas[2,64] (Table 3). While there is little information specifically related to all of these drug classes, it would be anticipated that DPP-4 inhibitors, SGLT-2 inhibitors, or GLP-1 analog medications would also be effective at normalizing blood glucose levels. Increases to therapy intensiveness to manage more severe glucose elevations would follow usual best practices for T2DM management, and patients may ultimately require insulin for optimal control in the short term.

The ICIs and 5-FU analog classes cause hyperglycemia due to varying degrees of insulin deficiency at the level of the pancreatic β-cell, and once present the diabetes is generally permanent[3,34,44] (Table 2). As discussed above, it is very important to continue glucose monitoring even after therapy has been completed with these two classes, as diabetes can develop for up to at least one year. To date, there is little direction surrounding the specific monitoring and management of hyperglycemia in patients treated with 5-FU, in contrast to multiple current guidelines available for the numerous autoimmune adverse effects of ICI, including IDD[18] (Table 3).

The diabetes developing as a result of 5-FU analog therapies has rarely led to DKA, suggesting that the insulin deficiency is not absolute in the great majority of cases (Table 1). This raises the possibility that sulfonylureas may have a beneficial role in mild glucose elevations due to their ability to enhance pancreatic β-cell insulin secretion; this increased release of insulin may compensate for the underlying low insulin levels and thereby normalize blood glucose levels. This has neither been specifically investigated nor reported, but their use could be rationalized based on the underlying defect driving hyperglycemia with 5-FU therapy.

Independent of ICI therapy, the majority of T1DM occurs in children or young adults, and there is a global all-age incidence of 15 per 100000 persons[107]. The 0.2%-4.9% incidence of insulin-deficient hyperglycemia in adults after ICI therapy (median age > 60 years years[1]) is higher than global rates and presents in older than expected age groups, suggesting that its development may be more complex than merely unmasking those at inherent risk for developing T1DM. Without doubt there are complexities not yet appreciated, yet it is not known how to identify those at highest risk for the development of T1DM with ICI use. As these therapies become more

Table 3 The underlying mechanisms and treatment considerations of hyperglycemia differ between chemotherapy classes

	Etiology of hyperglycemia	Treatment considerations
Glucocorticoids	Major: Insulin resistance	Oral hypoglycemics possible for mild
	Minor: Decreased insulin release	Consider selecting insulins with duration of action to match that of the steroid being given
5-FU and analogs	Major: Decreased insulin release and production	Diet or oral hypoglycemics for mild
		Insulin for severe
PI3K/mTOR inhibitors	Major: Insulin resistance	Diet or metformin for mild
Immune checkpoint inhibitors	Major: Profound insulin deficiency	Immediate initiation of insulin in new onset hyperglycemia
		Switch to insulin in pre-existing T2DM

5-FU: 5-fluorouracil; PI3K: Phosphatidyl inositol-3-kinase; mTOR: Mammalian target of rapamycin; T2DM: Type 2 diabetes mellitus.

widespread and cases rise, it may become more clear. At this time, it has been considered that the HLA-DR4 genotype and presence of other autoimmune diseases may correlate with increased risk[28].

For the ICI class, insulin therapy is essential in new onset diabetes given the extreme risk of IDD causing severe hyperglycemia and ketosis, reported to be as high as 77.8% [37]. Furthermore, insulin should be strongly considered in those with previous T2DM who fail to control their diabetes with ICI treatments, given the risk of a new underlying insulin deficiency. In patients with T2DM already taking non-insulin therapies, the initiation of a long acting basal insulin and rapid acting prandial insulin should be strongly considered, as simply adjusting their current medical therapy for T2DM may be ineffective as insulin-resistance may no longer be the main driving force for their hyperglycemia (Table 3). Insulin therapy would be necessary to reduce their risk of acute DKA in these cases[1].

CONCLUSION

Patient education regarding symptoms of hyperglycemia is an important safety component when initiating any of these medications, as are the more critical symptoms of hyperventilation and nausea or vomiting that may be associated with imminent DKA upon ICI therapy, in particular. The appearance of these symptoms should trigger an immediate evaluation for hyperglycemia, endogenous insulin levels (post-meal C-peptide and insulin), and acidosis/ketones to rule out developing DKA.

Given the consequences of uncontrolled blood sugars for these patients, it is important to recognize and manage hyperglycemia during cancer therapy, whether because of a worsening control of pre-existing diabetes or new onset hyperglycemia arising as a side effect of the chemotherapy itself. Current recommendations suggest tailoring glycemic control according to the underlying etiology of the hyperglycemia (insulin-resistance *vs* insulin-deficiency)[16] (Table 3) and to also consider that many cancer therapies are prescribed in cycles, which will require monitoring and perhaps intermittent treatment of the hyperglycemia[106].

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