Diabetes Risk with Immune Check Point Inhibitors and Glucocorticoids in Cancer Patient

2023 Diabetes Update

Anupam Kotwal, MD, MSc, FACE, FRCP (Edin)
Assistant Professor
Division of Diabetes, Endocrinology and Metabolism
Buffett Cancer Center
Emai: Anupam.Kotwal@unmc.edu
X: @DrAKotwal

University of Nebraska Medical Center

1

Disclosures

Consultant: Horizon Therapeutics USA, Inc.

2

Learning Objectives

- Understand the complex relationship between cancer, cancer therapies and hyperglycemia/diabetes
- Evaluate and manage hyperglycemia/diabetes from specific cancer therapies:
  - Immune checkpoint inhibitors (CPIs)
  - Glucocorticoids (steroids)
  - Phosphoinositide 3-kinase inhibitors (PI3KI)

3

Current Diabetes Reports (2021) 21:62
https://doi.org/10.1007/s11892-021-01435-y

HEALTH CARE DELIVERY SYSTEMS AND IMPLEMENTATION IN DIABETES (ME MCDONNELL AND AR SADHU, SECTION EDITOR)

Check for updates

Patient-Centered Diabetes Care of Cancer Patients

Anupam Kotwal[1] · Yee-Ming M. Cheung[2,3] · Grace Cromwell[3] · Andjela Drincic[1] · Houry Leblebjian[4] · Zoe Quandt[5] · Robert J. Rushakoff[5] · Marie E. McDonnell[3]

1. Division of Diabetes, Endocrinology and Metabolism, University of Nebraska Medical Center, Omaha, NE
2 Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia
3 Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115
4 Department of Pharmacy, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA
5 Division of Endocrinology and Metabolism, University of California, San Francisco, CA

Andjela Drincic, MD

4

Relationship Between Cancer and Hyperglycemia/Diabetes

Hyperglycemia/ Diabetes

Cancer risk (pancreas, colon, liver, breast, bladder)

Pioglitazone → bladder

Cancer

Therapies for cancer → hyperglycemia/diabetes

Mortality & morbidity

High insulin and glucose → tumor recurrence, metastasis, chemotherapy resistance

1. *Arcidiacono B, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res. 2012*
2. *Barone BB, et al. Postoperative mortality in cancer patients with preexisting diabetes. Systematic review and meta-analysis. 2010*
3. *Zeng L, et al. Hyperglycaemia confers resistance to chemotherapy on breast cancer cells: the role of fatty acid synthase. Endocr Relat Cancer. 2010*

5

Case 1

76 y/o M with multiple myeloma started on pembrolizumab (PD-1 inhibitor)

Hospitalized for weakness and confusion 3 weeks later

Diagnosed with **DKA**

- RPG 972 mg/dL
- HbA1c 7.8 %
- AG metabolic acidosis, Beta-hydroxybutyrate 5 mmol/L, ketonuria

Managed and discharged on basal-bolus insulin

On follow-up in 4 weeks

- C-peptide <0.1 ng/mL with PG 278 mg/dL
- 3 autoimmune diabetes Ab +

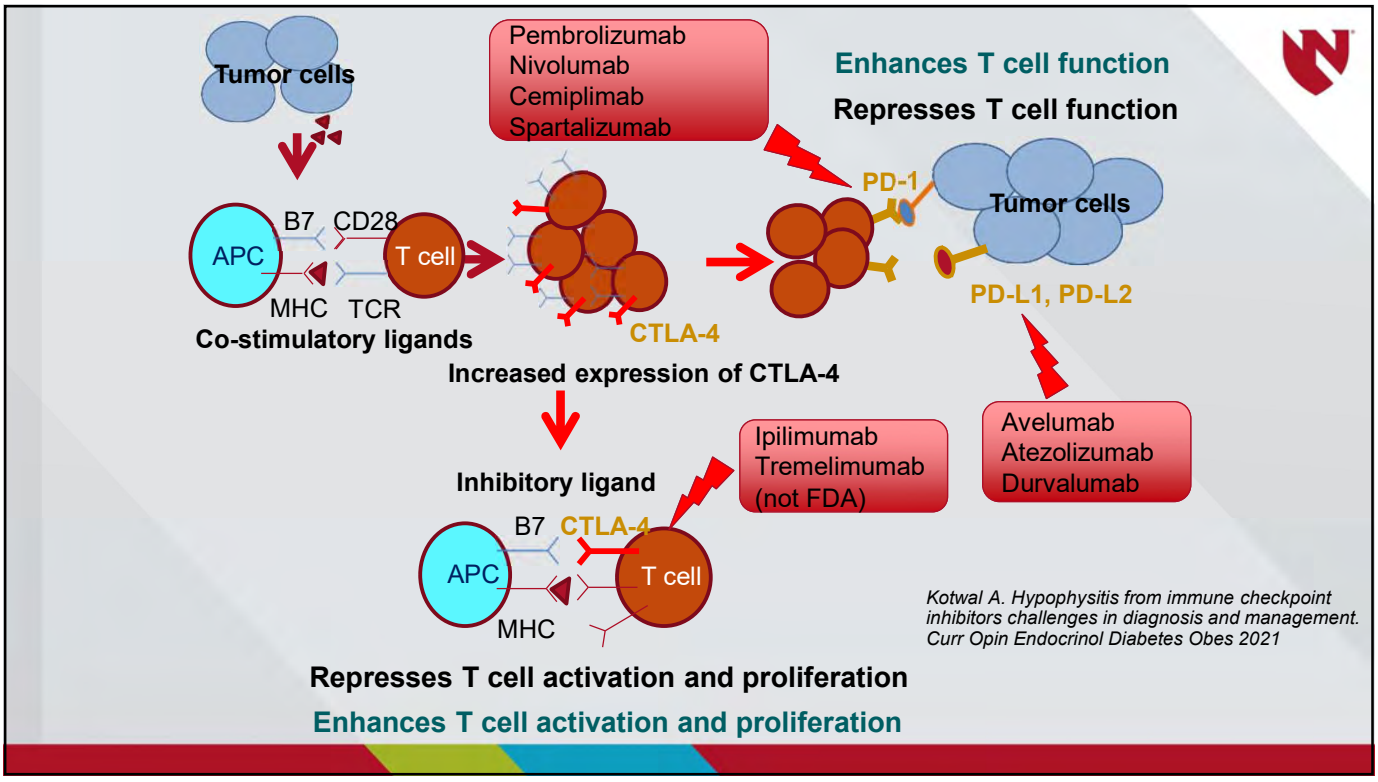
6

Poll Q1

New diabetes/hyperglycemia in the setting of immune checkpoint inhibitors is best managed by:

1. Basal-bolus insulin
2. Daily intermediate-acting insulin like NPH
3. Oral-antihyperglycemic agents
4. GLP-1 analogs

7



8

CPI-induced Diabetes: Pathogenesis

- T cell–mediated destruction of pancreatic β cells
- HLA class II association
  - 51.3% HLA-DR4 associated with classic type 1 diabetes
  - 14.1% HLA-DR9 associated with fulminant type 1 diabetes
  - 10.3% protective phenotypes for type 1 diabetes
- Histopathology of pancreas (n=1): peri-islet infiltration of CD8+ T cells like early-onset type 1 diabetes but almost complete absence of insulin-positive cells → ***severe nature of insulin deficiency***

1. *Mourad D, et al. Immune checkpoint inhibitor-induced diabetes mellitus: potential role of T cells in the underlying mechanism. Int J Mol Sci. 2021*
2. *Lo Preiato V, et al. Diabetes mellitus induced by immune checkpoint inhibitors: type 1 diabetes variant or new clinical entity? Review of the literature. Rev Endocr Metab Disord. 2021*
3. *Yoneda S, et al. T-lymphocyte infiltration to islets in the pancreas of a patient who developed type 1 diabetes after administration of immune checkpoint inhibitors. Diabetes Care. 2019*

9

CPI-induced Diabetes: Presentation

- Average age of presentation is in 60s
- Frequency: **PD-1/PD-L1**/combination (up to 2%) >>> CTLA-4
- Median time to onset 5 months (1 week to 2 years)
  - Several months even after CPI is stopped
- **New-onset** insulin deficiency or **worsening** hyperglycemia
- Some similarities to type 1 diabetes but more rapid progression to insulin deficiency like **Fulminant diabetes**
  - 2/3rd with DKA and low c-peptide
  - Glycemic variability

1. *Kotwal A, et al. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. BMJ Open Diabetes Res Care. 2019*
2. *Jeun,…Thosani S. Immunotherapy 2023*
3. *Lo Preiato V, et al. Diabetes mellitus induced by immune checkpoint inhibitors: type 1 diabetes variant or new clinical entity? Review of the literature. Rev Endocr Metab Disord. 2021*

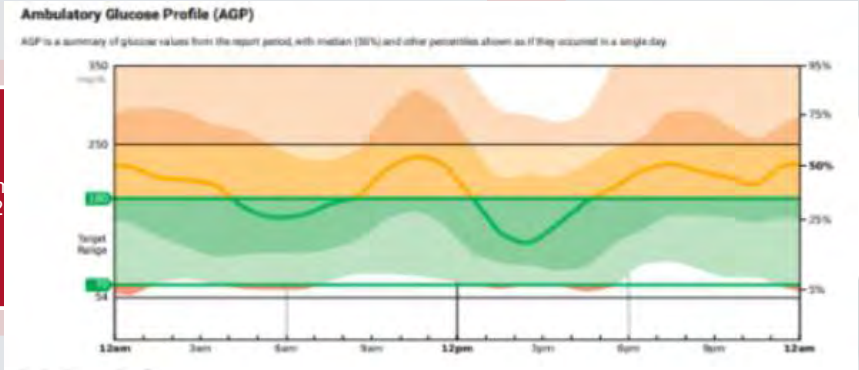
10

Case 2

45-year-old female with breast Ca sent by oncology for polyuria, polydipsia while on pembrolizumab (PD-1 inhibitor)

May 2021: Steroid-induced DM with HbA1c 9.4%; started Lantus + NPH, then on Lantus + Januvia, then to Lantus + GLP1 analog

Pembrolizu
started jan 2



Is this insulin-deficiency from PD-1 inhibitor?

11

Poll Q2

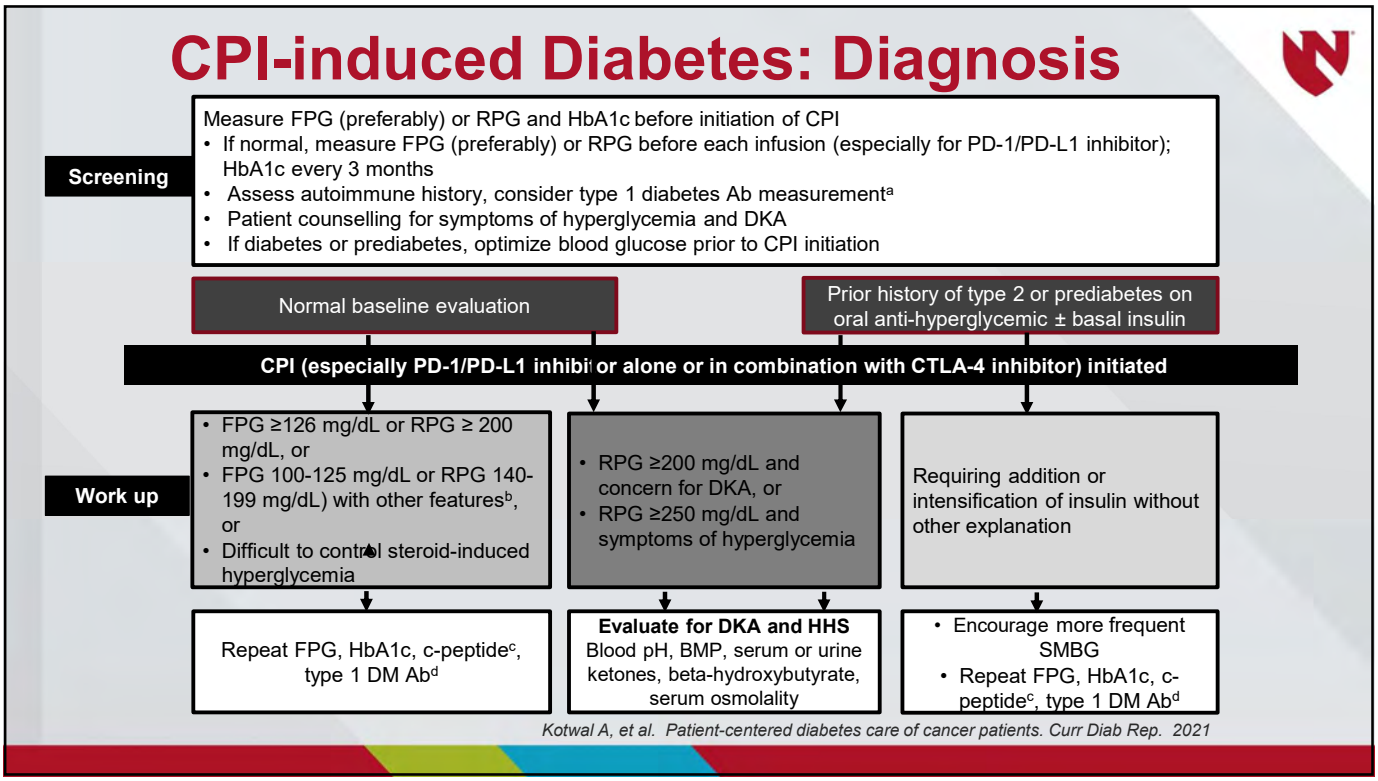
Significant basal-bolus insulin requirement and glycemic variability or low c-peptide after CPI but T1DM Ab- can still be CPI-induced insulin deficiency.

1. True
2. False

ICI-induced DM 30-50% Ab -ve

12

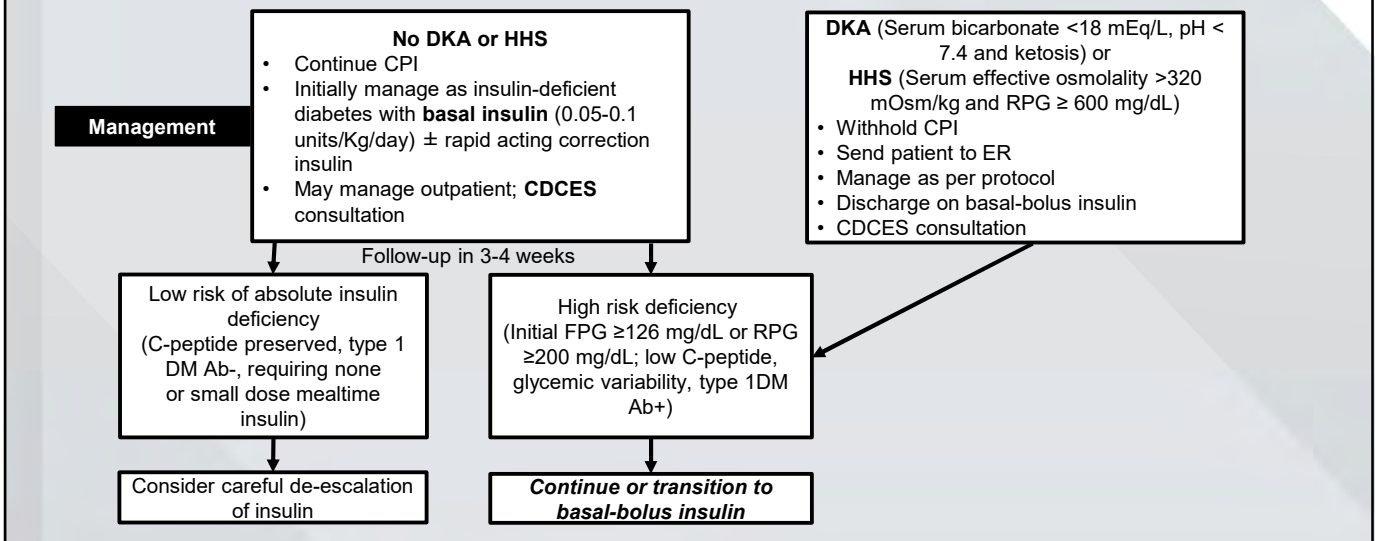
CPI-induced Diabetes: Diagnosis



Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

13

CPI-induced Diabetes: Management



Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

14

CPI-induced Diabetes: Management caveats

- ***Initially treat as insulin-dependent diabetes***
  - then adjust based on additional data
- Patients older, sicker and may get high dose steroids requiring frequent insulin changes
- Higher glycemic variability than classic type 1 diabetes
- ***Risk for rapid insulin deficiency and DKA***
- Glucocorticoids not useful (tried in n=4)
- ***Insulin deficiency usually persists***

Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

15

Poll Q1

New diabetes/hyperglycemia in the setting of immune checkpoint inhibitors is best managed by:

1. **Basal-bolus insulin**
2. Daily intermediate-acting insulin like NPH
3. Oral-antihyperglycemic agents
4. GLP-1 analogs

16

Poll Q2

Significant basal-bolus insulin requirement and glycemic variability or low c-peptide after CPI but T1DM Ab- can still be CPI-induced insulin deficiency.

1. **True**
2. False

ICI-induced DM 30-50% Ab -ve

17

Case 3

46-year-old female with AML s/p stem-cell transplant on prednisone 90 mg daily for GVHD. Weight 76 kg.

Plasma gluco
fasting am 18
random during
300s

18

Poll Q3

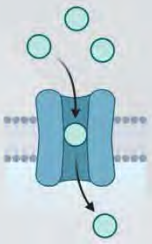
New-onset moderate hyperglycemia in the setting of daily prednisone use is best managed by:

1. Basal-bolus insulin
2. Daily intermediate-acting insulin like NPH +/- correction scale
3. Oral-antihyperglycemic agent like Glipizide or Repaglinide
4. GLP-1 analog

19

Steroid-induced Diabetes: Pathogenesis

- Induction of ***insulin resistance*** through down-regulation of glucose transporter 4 (GLUT4)



- Increased gluconeogenesis in the liver
- Decreased insulin secretion at the pancreatic islet cell
- Reduced binding of insulin to the insulin receptor

1. *Perez A, et al. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014*
2. *Oyer DS, et al. How to manage steroid diabetes in the patient with cancer. J Support Oncol. 2006*

20

Steroid-induced Diabetes: Presentation

- ***Post-meal hyperglycemia*** typically with prednisone ≥10 mg or dexamethasone ≥ 2 mg
- Steroids ***double the odds of type 2 diabetes***
  - 2-50% rate of hyperglycemia
- Risk factors: duration of treatment, increased age, increased weight, prior glucose intolerance, family history diabetes
- Best criterion is a random PG >200 mg/dL
  - Ideally SMBG both pre-meal and 2 h post-meal, especially ***focusing on lunch and dinner***

1. *Perez A, et al. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014*
2. *Tamez-Pérez HE, et al. Steroid hyperglycemia: prevalence, early detection and therapeutic recommendations: a narrative review. World J Diabetes. 2015*
3. *Oyer DS, et al. How to manage steroid diabetes in the patient with cancer. J Support Oncol. 2006*

21

Steroid-induced Diabetes: Diagnosis & Management

New Steroid-induced Diabetes

Glucose ≥ 140 mg/dL fasting or ≥ 200 mg/dL random[a], not on diabetes medication

Diet and exercise counselling, CDCES consultation, start SMBG before breakfast and dinner , start metformin unless contraindications

If persistent hyperglycemia with pre-dinner glucose >200 mg/dl for 2 or more weeks

Daily Steroids (Dexamethasone ≥ 2mg/ day or Prednisone ≥ 10mg/day)

Intermittent Dose Steroids (daily on and after treatment days)

Prednisone, Methylprednisolone: Dose medications below on every day glucocorticoids given

Dexamethasone: Dose medications below on every day dexamethasone is given plus 2 additional days

Glipizide 2.5mg prior to first meal of the day. Titrate up to 5mg for two meals per day, or
Repaglinide 2mg or Nateglinide 120mg prior to breakfast and lunch

Alternative (or if orals ineffective with glucose >200 mg/dl predinner after 2 weeks):
NPH Insulin prior to AM meal
Generally, can start with NPH 0.1 units per kg[b]

- Titrate up by 2 units every 1-2 days to achieve pre-dinner glucose < 200 mg/dL
- Add evening dose after 1 week if fasting glucose >180 mg/dL
- Titrate evening dose up by 2 units every 1-2 days to achieve fasting glucose < 180 mg/dL
- If steroid is intermittent, use response at last cycle to inform insulin dosing in next cycle

Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

22

Steroid-induced Diabetes: Diagnosis & Management

Prior History of Diabetes, Not on Insulin

Glucose ≥ 140 mg/dL fasting or ≥ 200 mg/dL random[a], adherent to diabetes medications

Daily Glucocorticoids

(Dexamethasone ≥ 2mg/ day or Prednisone ≥ 10mg/day)

Intermittent Dose Glucocorticoids (daily on and after treatment days)

- Prednisone, Methylprednisolone: Dose insulin on every day glucocorticoid is given
- Dexamethasone: Dose insulin on every day dexamethasone is given plus 2 additional days

NPH Insulin prior to AM meal added to usual DM regimen; CDCES consultation

- Generally, can start with NPH 0.15 units per kg[b]
- Titrate up by 2 units every 1-2 days to achieve pre-dinner glucose < 200 mg/dL
- Add evening dose after 1 week if fasting glucose >180 mg/dL
- Titrate evening dose by 2 units every 1-2 days to achieve fasting glucose < 180 mg/dL

Alternative or if NPH ineffective after 4 weeks: Use premixed insulin before AM meal

- Generally, can start with premixed 0.2 units per kg (or same dose as previous NPH, whichever is lower)[b]
- Titrate up by 2 units every 1-2 days to achieve pre-dinner glucose <200 mg/dL
- Add evening dose after 1 week if fasting glucose >180 mg/dL
- Titrate evening dose up by 2 units every 1-2 days to achieve fasting glucose < 180 mg/dL
- If steroid is intermittent, use response at last cycle to inform insulin dosing in next cycle

Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

23

Case 4

- 54-year-old M with prediabetes (HbA1c 6.2%) and non-small cell lung cancer was started on gemcitabine and cisplatin which required dexamethasone on the day of chemotherapy (day 1), and daily for the subsequent 2 days (days 2 and 3)
- Random PG 246 mg/dL and polyuria that interrupted his sleep
- SMBG before breakfast and dinner
  - Pre-breakfast: 162–196 mg/dL on days 2, 3, and 4; 128–156 mg/dL on day 5 and beyond
  - Pre-dinner: 268 to 395 mg/dL on day 1, 2 and 3; 190–220 mg/dL on day 4; <200 mg/dL by day 5

24

Poll Q4

New diabetes/hyperglycemia in the setting of daily dexamethasone use is best managed by:

1. Twice daily intermediate-acting insulin like NPH or once daily long-acting insulin like glargine +/- correction scale
2. Daily intermediate-acting insulin like NPH
3. Oral-antihyperglycemic agents
4. GLP-1 analogs

25

Steroid-induced Diabetes: Management caveats

- Consider steroid pharmacokinetics, steroid dose, frailty, weight, food intake, and renal function
  - For example, insulin required up to 2 days after dexamethasone
- ***NPH usually with daily prednisone*** to cover post-prandial BG
  - RCTs of NPH vs. MDI in hospital setting do not show superiority
- For patients already on insulin: focus on increasing ***prandial coverage*** by increasing basal 25%, each mealtime 30–50%
- *Caveat*: Severe hyperglycemia without prior data, consider hospitalization and IV insulin to assess need

1. *Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021*
2. *Aberer F, et al. A practical guide for the management of steroid induced hyperglycaemia in the hospital. J Clin Med. 2021;10(10):2154.*

26

Improving Hyperglycemia Management in Cancer Patients Project

NEBRASKA MEDICINE Guild

Awarded $5000
Sample: 16 cancer patients with steroid-induced hyperglycemia/diabetes
CGMs provided
100% continuation rate

Anne Knape, APRN-NP

Melissa Lockard, CDCES

27

Poll Q3

New-onset moderate hyperglycemia in the setting of daily prednisone use is best managed by:

1. Basal-bolus insulin
2. **Daily intermediate-acting insulin like NPH +/- correction scale**
3. Oral-antihyperglycemic agent like Glipizide or Repaglinide
4. GLP-1 analog

28

Poll Q4

New diabetes/hyperglycemia in the setting of daily dexamethasone use is best managed by:

1. **Twice daily intermediate-acting insulin like NPH or once daily long-acting insulin like glargine +/- correction scale**
2. Daily intermediate-acting insulin like NPH
3. Oral-antihyperglycemic agents
4. GLP-1 analogs

29

Case 5

53-year-old F with metastatic breast cancer and no history of diabetes started alpelisip (PI3KI)

- SMBG rising 200-260 mg/dL a week later
- Empagliflozin 10 mg daily started but hyperglycemia uncontrolled
- Insulin detemir 0.2 units/kg QHS + empagliflozin 20 mg daily → achieved average SMBG <200 mg/dL
- Disease progressed, alpelisib and diabetes therapies were stopped
- One week later fasting PG again <100 mg/dL.

30

Poll Q5

New-onset moderate hyperglycemia in the setting of PI3 Kinase inhibitor use can initially be managed by:

1. Basal-bolus insulin
2. Daily intermediate-acting insulin like NPH
3. Oral-antihyperglycemic agent such as metformin
4. Oral-antihyperglycemic agent such as glipizide
5. GLP-1 analogs

31

PI3KI-induced Diabetes: Pathogenesis

- ***PI3Kα isoform***
  - mediates uptake of glucose into skeletal and adipose tissues
  - regulates hepatic glycogenolysis and gluconeogenesis
- Four FDA-approved PI3KIs:
  - ***Alpelisib*** and ***Copanlisib*** target PI3Kα isoform → insulin resistance and hyperglycemia
  - Idelalisib and Duvelisib usually do not affect glycemic control

Goncalves MD, et al. Phosphatidylinositol 3-kinase, growth disorders, and cancer. N Engl J Med. 2018;379(21):2052–62

32

PI3KI-induced Diabetes: Presentation

- Hyperglycemia is the ***most reported (50–64%)*** adverse effect of PI3Kα inhibitors
- Risk factors: pre-existing type 2 diabetes and maximum fasting PG >153 mg/dL at baseline, BMI>25 kg/m^2, Asian race
- Alpelisib: fasting PG generally peaks within the first 2 weeks
- Copanlisib: transient hyperglycemia where PG peaks 5-8 hours post-infusion and returns to baseline prior to the next infusion

1. *Shields M, et al. A systematic review and meta-analysis of selected toxicity endpoints of alpelisib. Oncotarget. 2020*
2. *Goldman JW, et al. Hyperglycemia associated with targeted oncologic treatment: mechanisms and management. Oncologist. 2016*
3. *Rugo HS, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with Hrpositive advanced breast cancer. Ann Oncol. 2020*

33

PI3KI-induced Diabetes: Diagnosis

Screening

Measure FPG and HbA1c before initiation of PI3KI
- If initially normal, measure FPG weekly for the first 2 weeks and then monthly thereafter for alpelisib and RPG pre and post each infusion for copanlisib; measure HbA1c every 3 months
- If diabetes or prediabetes, optimize blood glucose prior to initiation

PI3KI initiated

Mild hyperglycemia	Moderate hyperglycemia	Severe hyperglycemia	Life-threatening hyperglycemia
• CTCAE 1: FPG 140-159 mg/dL or • RPG < 200 mg/dL	• CTCAE 2: FPG 160-249 mg/dL or • RPG 200 - 299 mg/dL	• CTCAE 3: FPG 250-500 mg/dL or • RPG 300 - 599 mg/dL	• CTCAE 4: FPG ≥ 500 mg/dL or • RPG ≥ 600 mg/dL

Work up

Repeat FPG, HbA1c (if not recorded in past 3 months)

Evaluate for DKA and HHS
Blood pH, BMP, serum or urine ketones, beta-hydroxybutyrate, serum osmolality

Management
- Continue PI3K inhibitor
- No anti-hyperglycemic agents required
- Routine follow up with PCP/oncology

Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

34

PI3KI-induced Diabetes: Management

Management

No DKA or HHS
- Educate on lifestyle modifications; CDCES consultation
- Glucometer education/commence home SMBG
- Aim FPG <160 mg/dL and RPG <200 mg/dL

Moderate hyperglycemia
- Start metformin if SMBG remains above target
- Reduce alpelisib dose if FPG remains >160 mg/dL after 3 weeks
- Withhold copanlisib until FPG <160 or RPG <200 mg/dL

Moderate/severe hyperglycemia
- Start metformin[b]
- Consider adding second agent[c]
- Withhold alpelisib for 3-5 days and restart at a lower dose
- Withhold copanlisib until FPG <160 or RPG <200 mg/dL

Life-threatening hyperglycemia
- Send patient to ER
- Intravenous fluids
- Withhold PI3KI
- Manage with rapid-acting insulin
- Discharge on basal[a] insulin AND consider rapid-acting insulin with meals

DKA (Serum bicarbonate <18 mEq/L, pH < 7.4 and ketosis)
or
HHS (Serum effective osm >320 mOsm/kg and RPG ≥ 600 mg/dL)
- Withhold PI3K inhibitor
- Send patient to ER
- Manage as per protocol
- Discharge on basal[a]-bolus insulin
- CDCES consultation

If PI3KI is withheld or permanently ceased (relevant to alpelisib only)

If on anti-hyperglycemic agents
- Immediately stop all hypoglycemia-causing agents (insulin, sulfonylureas)
- Continue other anti-hyperglycemic agents for 1-2 weeks while glucose improves
- Cease all anti-hyperglycemic agents once blood glucose levels normalize

Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021

35

PI3KI-induced Diabetes: Management caveats

- Only approved for advanced disease → ***glycemic targets more lenient*** than for CPIs and steroids
- ***Prioritize insulin sensitizers***: metformin remains the most utilized in clinical trials to improve insulin sensitivity
- ***Minimize use of agents that activate insulin-signaling pathways***: avoid sulfonylureas (glipizide, glimepiride, etc.)
  - endogenous insulin & hyperinsulinemia linked to tumor growth
- Use insulin if necessary to achieve SMBG <200 mg/dL

1. *Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021*
2. *Busaidy NL, et al. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. J Clin Oncol. 2012*
3. *Lawrence RD. Renal threshold for glucose: normal and in diabetics. Br Med J. 1940*

36

Poll Q5

New-onset moderate hyperglycemia in the setting of PI3 Kinase inhibitor use can initially be managed by:

1. Basal-bolus insulin
2. Daily intermediate-acting insulin like NPH
3. **Oral-antihyperglycemic agent such as metformin**
4. Oral-antihyperglycemic agent such as glipizide
5. GLP-1 analogs

37

General Assessment before CPI/Steroid/PI3KI

- Family and personal history of diabetes and autoimmunity
- *Plasma glucose (PG)* (fasting if possible) and hemoglobin A1c (HbA1c)
- ***HbA1c maybe unreliable***; fructosamine if normal renal function
  - rapid onset of hyperglycemia
  - hematologic abnormalities: anemia or transfusions
- ***Counseling*** about symptoms of hyperglycemia and DKA
- Treat newly diagnosed diabetes before starting CPI/steroid/PI3KI
- For established diabetes → self-monitoring of blood glucose (SMBG) and/or continuous glucose monitor (CGM)

1. *Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021*
2. *Davis GM, et al. Diabetes technology in the inpatient setting for management of hyperglycemia. Endocrinol Metab Clin N Am. 2020*

38

General Principles of Management

- ***Prevent hypoglycemia, severe hyperglycemia, ketosis***
- ADA goals for older adults: pre-meal 90–130; post-meal ≤180 mg/dL
- Patients with reduced life expectancy: lenient glycemic targets
- Stable patients: best possible glycemic status without hypoglycemia
- Common Terminology Criteria for Adverse Events (CTCAE) is preferred by oncologists to grade the severity of hyperglycemia and other adverse events from cancer therapy
  - ***Any degree of hyperglycemia in CPI-treated patients warrants urgent evaluation*** *for insulin deficiency*

1. *Kotwal A, et al. Patient-centered diabetes care of cancer patients. Curr Diab Rep. 2021*
2. *Perez A, et al. Glucocorticoid-induced hyperglycemia. J Diabetes. 2014*
3. *American Diabetes Association. Older adults: standards of medical care in diabetes—2021Diabetes Care. 2021*

39

Endocrinology-Oncology referral (outpatient)


Whitney Goldner, MD


Anery Patel, MD


Anne Knape, APRN-NP


Anupam Kotwal, MD


Dorotha Rohlfsen, CDCES

40

Care of the Cancer Patient with Diabetes: Concluding Remarks

- *"Meet patients where they are"* to improve quality of life
- Cancer therapies impact glucose variably
  - CPIs: rapidly recognize insulin deficiency to prevent DKA
  - Steroids: eye on dose changes for glycemic variability
  - PI3KIs: milder hyperglycemia but may require insulin
- Intensive → maintenance therapy → survivorship: inter-disciplinary team approach to *Oncoendocrinology*

41