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Management of phosphoinositide 3-kinase inhibitor-induced hyperglycemia: A targeted literature review

Nikhil Bhatia, Eunice Kim, Anna Cheng, Yolande Du Toit

Genentech, Inc., San Francisco, CA

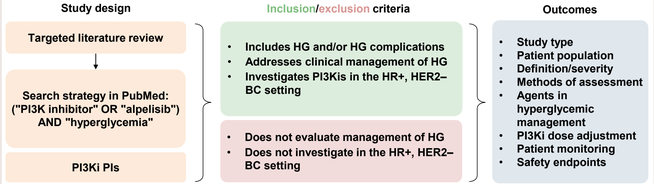
BACKGROUND

- Phosphoinositide 3-kinase inhibitors (PI3Kis) act on a pathway that drives cell growth, proliferation, and survival, and are used in treatment for multiple cancers.[1]
- However, this drug class in breast cancer (BC) is associated with hyperglycemia (HG), which was the most common grade 3 and 4 adverse event (AE) associated with alpelisib,[2] the only approved PI3Ki for BC.[3,4]
- Gaining a better understanding of published data regarding management of HG can enhance provider decision-making and patient care.
- The objective of this targeted literature review is to understand existing recommendations and real-world management of PI3Ki-induced HG among patients with *PIK3CA*-mutated (*PIK3CA*mut), hormone receptor-positive (HR+), HER2-negative (HER2–) BC.

METHODS

- A targeted literature review was conducted using PubMed for peer-reviewed studies published between August 2005 and September 2023; and it included HG and/or HG complications, addressed its clinical management, and included PI3Kis in the HR+, HER2– BC setting (Figure 1).
- Package inserts (PIs) for PI3Kis in BC addressing management of HG were also considered.

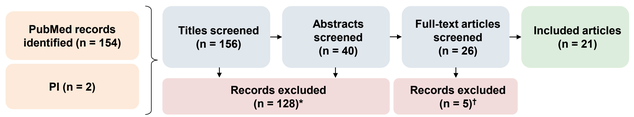
Figure 1: Methods



BC, breast cancer; HER2–, HER2-negative; HG, hyperglycemia; HR+, hormone receptor-positive; PI, package insert; PI3K(i), phosphoinositide 3-kinase (inhibitor).

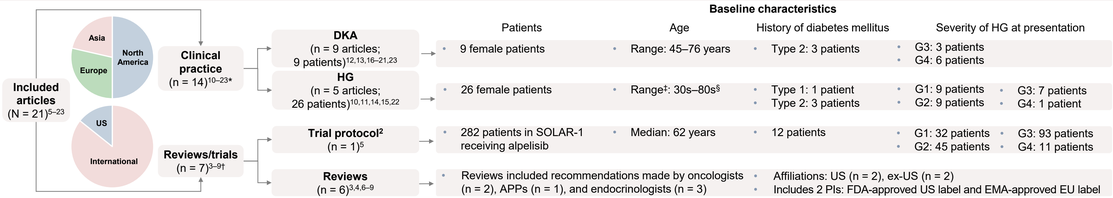
RESULTS

Figure 2: PRISMA flow diagram



* Does not evaluate management of HG (n = 106); does not investigate in the HR+, HER2– BC setting (n = 21); duplicates (n = 1).
† Does not evaluate management of HG (n = 3); not peer-reviewed or article paywalled (n = 2).
BC, breast cancer; HER2–, HER2-negative; HG, hyperglycemia; HR+, hormone receptor-positive; PI, package insert.

Figure 3: Summary of article breakdown



* North America (US, Canada), n = 7 (24 patients); Europe (France, Spain, Germany), n = 4 (8 patients); Asia (Lebanon, Qatar, United Arab Emirates), n = 3 (3 patients). † International (n = 6); US (n = 1).
‡ Lower and upper ends of range reflect unspecified ages found within data. §Only median age (59.7) was included in Burnette SE, *et al.* 2023.[10]
APP, advanced practice provider; DKA, diabetic ketoacidosis; EMA, European Medicines Agency; FDA, US Food and Drug Administration; G, grade; HG, hyperglycemia; PI, package insert.

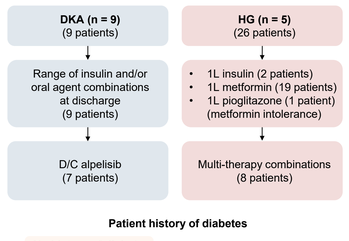
- Key findings from review and clinical practice reports are shown in Table 1 and Figure 4, respectively. In eight studies, HG was graded on a 1–4 scale (National Cancer Institute Common Terminology Criteria for Adverse Events v4.03).
- PI3Ki dose adjustments in non-PI reviews (n = 5) corresponded to the specific grade of HG as listed in the PIs (n = 2):
  - Grade 1: no dose adjustment | grade 2: reduce by one dose level if grade 1 is **not** reached within 21 days | grade 3: discontinue agent, if grade 1 is reached within 3–5 days, restart at lowered dose; if grade 1 is **not** reached within 21 days, permanently discontinue agent | grade 4: discontinue agent, if grade 3 is reached within 24 hours, follow grade 3 guidelines; if grade 3 is **not** reached within 24 hours, permanently discontinue agent.
- Management recommendations in clinical practice reports were generally consistent with management recommendations in reviews for three patients: metformin ± sodium/glucose cotransporter 2 inhibitors/thiazolidinediones ± insulin.

Table 1: Clinical interventions for PI3Ki-induced HG in articles (n = 7)[3–9]

	Clinical interventions		
	Lifestyle modification	Specialist consultation	Pharmacotherapy
Prevention*†	• Carbohydrate-restricted diet (n = 6 articles) • Exercise (n = 6 articles) • Tobacco cessation (n = 1 article)	• Endocrinologist consultation generally recommended at this stage (n = 4 articles); specifically recommended for patients at high risk for HG (n = 1 article)	• Metformin as a 1L agent if patient is at high-risk for HG (n = 1 article) • Pioglitazone as a 1L agent if patient is at high-risk for HG (n = 1 article)
G1†	• Carbohydrate-restricted diet (n = 1 article)		• Metformin specifically recommended as a 1L agent (n = 6 articles) • Thiazolidinediones and DPP-4i are 1L options (n = 3 articles)
G2	• Adequate hydration added (n = 2 articles)	• Endocrinologist consultation recommended at this stage (n = 1 article)	• Initiate/intensify metformin (n = 6 articles) • SGLT2i recommended as an additional agent (n = 4 articles) • Pioglitazone recommended as an additional agent (n = 6 articles) • DPP-4i recommended as an additional agent (n = 5 articles) • GLP-1 RAs recommended as an additional agent (n = 3 articles) • Alpha-glucosidase inhibitors (n = 2 articles)
G3 /G4	• Adequate hydration ensured (n = 4 articles)	• Endocrinologist consultation recommended at this stage (n = 5 article)	• Maximize metformin (n = 6 articles) • Multi-therapy combination recommended (n = 6 articles) • SGLT2i recommended as an additional agent (n = 4 articles) • Thiazolidinediones recommended as an additional agent (n = 6 articles) • DPP-4i recommended as an additional agent (n = 5 articles) • GLP-1 RAs recommended as an additional agent (n = 3 articles) • Alpha-glucosidase inhibitors recommended as an additional agent (n = 1 article) • Insulin can be used as a short-term‡ additional agent (n = 6 articles) • Meglitinides recommended as a 3L agent (n = 2 articles) • Sulfonylureas recommended as a 3L agent (n = 2 articles)

* Lifestyle modification prevention measures persist throughout possible progression from G1 to G4 HG.
† Numbers overlap between prevention and G1 sections.
‡ 1–2 days.
1L, first line; 3L, third line; DPP-4, dipeptidyl peptidase-1; G, grade; GLP-1, glucagon-like peptide-1; HG, hyperglycemia; PI3K, phosphoinositide 3-kinase inhibitor; RA, receptor agonist; SGLT2i, sodium/glucose cotransporter 2 inhibitor.

Figure 4: Management of PI3Ki-induced DKA/HG in clinical practice articles[10–23]*



* All HG events in the case reports were related to alpelisib.
† Patients at high risk for HG: history of diabetes, pre-diabetes, aged >75 years, BMI >30 kg/m^2.
1L, first line; BMI, body mass index; D/C, discontinue; DKA, diabetic ketoacidosis; HG, hyperglycemia; PI3Ki, phosphoinositide 3-kinase inhibitor.

Key takeaways

- Management can differ by types of anti-diabetic agents used and the timing of interventions based on factors such as diabetic status and risk of HG.
- The general trend of clinical interventions for HG consists of first-line metformin (n = 6 reviews/trials; 19 patients found in clinical practice), followed by oral antihyperglycemic agents (n = 6 reviews/trials; 8 patients found in clinical practice), and last-line insulin rescue (n = 3 reviews/trials; 4 patients in clinical practice).
- PI3Ki dose adjustments correspond to HG grade (n = 7 reviews/trials; 20 patients in clinical practice).
- Management can be slightly different between patients at high and low risk for HG (n = 2).
- Endocrinologists were recommended to be consulted in patients with HG.
  - Patients at higher risk for HG before initiation of alpelisib were recommended to consult an endocrinologist in four reviews/trials.
  - Endocrinologists were specifically recommended to be consulted in cases of grade 3/grade 4 HG in six reviews/trials.
- Lifestyle modifications were recommended in HG management, including: a carbohydrate-restricted diet (n = 6 reviews/trials), exercise (n = 6 reviews/trials), and adequate hydration (n = 4 reviews/trials).

Limitations

- Small sample size of included studies.
- Heterogeneity between included studies.
- Case reports included female patients only.
- HG graded by primary researcher in selected studies.

CONCLUSIONS

- **In available recommendations and real-world management, there was an observed trend of metformin followed by oral antihyperglycemic agents and insulin rescue, if necessary.**
- **PI3Ki dose adjustments followed a protocol corresponding with HG grade.**
- **Differences in management can exist between patients at high and low risk of HG, as well as in timing of endocrinologist consultations.**
- **The findings of this literature review can improve provider decision-making and patient outcomes.**

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CONFLICTS OF INTEREST

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