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Diabetes and Oncological Therapies:

Management and Multidisciplinary Approach

Cancer and diabetes mellitus (DM) represent two health problems that frequently coexist. The incidence and prevalence of both are increasing rapidly worldwide: 1 in 5 patients diagnosed with cancer has DM (1, 2).
DM can represent a risk factor for different malig-

nant tumors or neoplasms, such as those of the pancreas, colon, liver, breast, and endometrium, and can worsen the clinical course of patients with cancer.

Patients with diabetes and cancer face specific problems.

Some antineoplastic drugs cause an increase in blood glucose, which can induce a decrease in the efficacy of cancer treatments. Both the drugs used to control cancer symptoms and those for the prevention and treatment of side effects of antineoplastic drugs also increase blood glucose (1).

On the other hand, the impact of a cancer diagnosis can affect adherence to DM treatment.

Certain complications related to DM (chronic kidney disease, cardiovascular disease, peripheral neuropathy) can limit the use or require dose adjustments of some antineoplastic drugs, resulting in a lower response. Therefore, the mortality rate may be increased in the diabetes and cancer combination (3).

EPIDEMIOLOGY

Common risk factors for DM and some types of cancer are age, a diet high in saturated fats, obesity, sedentary lifestyle, and smoking. The incidence and prevalence of both diseases have increased in parallel in recent years. It is estimated that currently more than 450 million people worldwide have diabetes, while approximately 19 million people are affected by some type of cancer (excluding non-melanoma skin cancer).

Cancer mainly affects older people: 60% of new diagnoses occur in individuals older than 65 years. On the other hand, 25% of people older than 65 develop type 2 diabetes mellitus (T2DM). In addition, between 8% and 20% of cancer patients also suffer from T2DM, this percentage varying according to the type of neoplasm (4).

RELATIONSHIP BETWEEN DIABETES MELLITUS AND CANCER

Hyperglycemia, insulin resistance, and elevated insulin levels (and other growth factors) can increase the risk of developing cancer or worsen an existing one.

Insulin is not only a hormone that controls blood sugar but can also stimulate cell division. In T2DM, if insulin levels are elevated, this alteration can promote tumor growth.

Obesity, with the accumulation of adipose or fatty tissue, is closely related to T2DM. Increased fat favors an increase in peripheral estrogen levels, an increase in the production of reactive oxygen species, and a state of chronic inflammation. Deregulation of sex hormones, oxidative stress, and the high presence of pro-inflammatory cytokines favor uncontrolled cell proliferation, which can lead to cancer.

The microbiota is a community of living microorganisms residing in a specific ecological niche, such as the human intestine (colon). The microbiome is defined as a complex network of interactions that these microorganisms establish with our cells, both in physiological or normal situations and in the development of some diseases (5). The relationship between the digestive microbiome, diabetes, and cancer is under study. It has been found that alteration of the digestive microbiome, produced by both external (diet) and internal (cytokines) factors, is related to insulin resistance and the appearance of different types of gastrointestinal neoplasms such as those of the liver, pancreas, and colon.

DM can worsen the prognosis of patients with cancer. Some epidemiological studies have found a linear association between blood glucose concentration and mortality related to certain types of cancer (3).

In patients with DM and cancer, antineoplastic treatment may differ from the standard: either because the reference drugs are contraindicated in diabetes or because it is necessary to use them at lower doses to reduce side effects. Patients with diabetes may have more diarrhea, leukopenia, and thrombocytopenia (low white blood cells and platelets) or hypocalcemia (low blood calcium levels), among other side effects characteristic of cancer treatments. They also have a higher risk of complications arising from infections or cardiovascular events.

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DRUG CATEGORY	EXAMPLES	MECHANISM OF ACTION	EFFECT ON GLUCOSE METABOLISM	GLYCEMIC MANAGEMENT
Immunotherapy	Anti-CTLA-4 (ipilimumab), Anti-PD-1/PD-L1 (pembrolizumab, nivolumab)	Destroys pancreatic beta cells via immune system activation	Decreased insulin synthesis.	Regular glucose monitoring. Consider initiating insulin if autoimmune diabetes develops.
PIK3CA/AKT/mTOR Pathway Inhibitors	PI3K inhibitors (alpelisib), AKT inhibitors (ipatasertib, capivasertib), mTOR inhibitors (everolimus, temsirolimus)	Block cellular response to insulin	Impaired glucose control.	Adjust oral antidiabetics or insulin therapy as needed.
IGF-1R Inhibitors	Anti-IGF-1R (linsitinib, dalotuzumab)	Block insulin receptor	Hyperglycemia due to partial inhibition of insulin action.	Strict glucose control, possible insulin requirement. Evaluate insulin resistance.
EGFR Inhibitors	Anti-EGFR (rociletinib, cetuximab, panitumumab)	Block EGFR, which is part of the insulin receptor family	Hyperglycemia of uncertain mechanism.	Regular glucose monitoring. Consider antidiabetics/insulin if significant hyperglycemia.
Multikinase Inhibitors	Nilotinib, dasatinib, ponatinib	Block kinases that activate the PI3K/AKT/mTOR pathway	Decreased insulin response, impaired glucose control.	Regular glucose monitoring. Increase insulin or adjust treatment as needed.
Hormonal Therapy	Anti-estrogens (tamoxifen, aromatase inhibitors), Antiandrogens (bicalutamide)	Reduce insulin secretion and increase triglycerides. Modulate androgen receptor activity in liver and adipocytes	Insulin resistance and hypertriglyceridemia.	Weight control and low-carb diet. Consider antidiabetics/ insulin if needed.
Corticosteroides	Prednisona, dexametasona.	Aumentan la liberación de glucosa y disminuyen la síntesis y liberación de insulina.	Hiperglucemia transitoria o persistente.	Monitorización frecuente de glucemia. Uso de insulina basal y rápida si es necesario. Reducción gradual de dosis de corticoides si es posible.

TABLE 1: Effects of antineoplastic drugs on carbohydrate metabolism

» INTERACTION AMONG DIABETES, CANCER, AND THEIR TREATMENTS

There is no evidence to confirm that insulin, the basis of treatment for T1DM and also used in some cases of T2DM, increases the risk of cancer. Regarding other non-insulin antidiabetic drugs, studies have shown varied and unclear results. There are preclinical and epidemiological studies that demonstrate an "antineoplastic effect" of metformin (widely used in patients with T2DM), yet this has not been confirmed by randomized clinical trials (1).

There are different types of drugs to treat cancer: cytotoxic chemotherapy, hormone therapy, targeted therapy, and immunotherapy. Some of these agents and other additional drugs used to control side effects (for example, drufs used to prevent or treat nausea and vomiting) can affect glycemic control. This effect may be due to different mechanisms: increased circulating glucose levels, decreased insulin production by pancreatic beta cells, or peripheral insulin resistance similar to that observed in T2DM.

Table 1 summarizes the main antineoplastic drugs and their mechanisms of action with effects on carbohydrate metabolism, as well as how to address blood glucose. These drugs are used in numerous types of cancer. D

CONCLUSIONS

Before starting antineoplastic treatment or glucocorticoids, it is important to determine baseline blood glucose and glycated hemoglobin (HbA1c) in cancer patients. Previous complications of DM should be evaluated in patients with diabetes, and information should be provided about the risk of hyperglycemia, as well as providing means of glycemic control if necessary (6). Similarly, dietary interventions will be emphasized: reducing carbohydrate consumption and avoiding foods with a high glycemic index. If nephrotoxic or hepatotoxic antineoplastic drugs are administered, it may be necessary to adjust hypoglycemic treatment.

In general, the hypoglycemic agents used in DM (metformin, gliptins and thiazolidinediones, DPP4 inhibitors, GLP-1 receptor agonists, and insulin) are considered safe, although the impact of the "non-glycemic effects" of these drugs in the oncology population differs from the impact in the general population, which justifies individualizing treatment in patients with cancer and diabetes.

In palliative care, the management of glycemic control should be individualized, prioritizing risk reduction and ensuring patient well-being. It is recommended to minimize glucose monitoring and consider deprescribing hypoglycemic drugs when appropriate.

The approach should be multidisciplinary in patients with cancer and hyperglycemia, creating a collaborative space between oncology, family medicine, endocrinology, and hospital pharmacy (which carries out the review and active monitoring of drug interactions).

SOME EPIDEMIOLOGICAL STUDIES HAVE FOUND A LINEAR ASSOCIATION BETWEEN BLOOD GLUCOSE CONCENTRATION AND MORTALITY RELATED TO CERTAIN TYPES OF CANCER

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