Management of Diabetes and Pancreatic Cancer

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A 54-year-old male patient named D.N. developed type 2 diabetes mellitus (T2DM) 10 months ago. At the time, he weighed 225 pounds and had a body mass index of 35.2. D.N. was started on metformin with poor control and, within two months, glimepiride was added to his regimen. Six months later, D.N.'s hemoglobin A1c (HbA1c) was still above 8% (normal is less than 6%), so his endocrinologist added exenatide. He had a fairly well controlled fasting blood glucose and HbA1c ranging from 6.5%–7.3% after exenatide was added. One month later, however, D.N. developed abdominal pain and anorexia with a 20-pound weight loss. His blood glucose became extremely labile despite his poor oral intake and good compliance with his oral hypoglycemic agents.

A few days later, D.N. presented to the emergency room with severe abdominal pain and difficulty eating. An abdominal ultrasound revealed a normal pancreas, but a computed tomography (CT) scan showed evidence of pancreatitis and a possible mass in the tail of the pancreas. D.N. was first treated for pancreatitis and then underwent an endoscopic ultrasound that revealed an irregular partially cystic mass that was 2 x 3 cm in size. Multiple biopsies showed atypical cells. A distal pancreatectomy was performed and pathology revealed pancreatic intraepithelial neoplasia with high-grade dysplasia with a question of invasive adenocarcinoma; findings by two independent pathologists were inconclusive. Thirteen peripancreatic lymph nodes were negative for metastatic tumor. D.N. was observed for two months and a repeat CT scan revealed a recurrent mass in the pancreatic surgical bed with invasion of the hepatic artery and superior mesenteric vein. An ultrasound-guided biopsy confirmed adenocarcinoma, and D.N. was referred to a medical oncologist for treatment

options. Diabetes management also was very difficult at this point as his blood glucose was consistently greater than 300 mg/dl (normal is less than 125 mg/dl) despite oral medications and a 70-pound weight loss. Pancreatic insufficiency caused by his surgery and disease resulted in chronic diarrhea and further malnutrition.

The decision was made with the patient and family to initiate fluorouracil, leucovorin, and oxaliplatin chemotherapy. This regimen presented a few challenges because oxaliplatin and all supportive fluids are mixed in dextrose and the recommended antiemetic regimen includes dexamethasone, a glucocorticoid. This combination puts additional burden on glucose metabolism.

Although nausea can be fairly well controlled, anorexia and taste changes can reduce caloric intake and affect insulin and oral hypoglycemic medication requirements. D.N. tolerated the first cycle well with minimal nausea, but his blood sugar rose above 500 mg/dl and his lactic acid level was elevated; therefore, he was hospitalized for stabilization of his glucose. Working with his endocrinologist, D.N. was initiated on a regimen with sliding scale regular insulin (humulin) and metformin, which helped maintain glucose control.

Type 2 Diabetes and Pancreatic Cancer

The case study illustrates a few of the many interactions between diabetes, specifically T2DM, and pancreatic cancer. As in the case study, the onset of diabetes within two years of pancreatic cancer may be related to the cause of the pancreatic cancer or a result of its development. Pancreatic cancer can induce diabetes through islet cell destruction and increasing insulin resistance by elevating plasma levels of islet amyloid polypeptide, a hormone that may cause

insulin resistance (Permert et al., 1994). T2DM is a disease of insulin resistance, impaired insulin production, and increased glucose production (Singer, 2007).

Assessment

When a patient is first diagnosed with pancreatic cancer, a thorough assessment is performed to identify comorbidities and issues that will help determine treatment strategy. Patients should be assessed for risk factors associated with the development of diabetes prior to the initiation of cancer therapy. These risk factors include age, obesity, family history of diabetes, history of gestational diabetes, and a previously abnormal fasting glucose or glucose tolerance test. If the patient has any of these risk factors, fasting glucose and HbA1c should be included in the initial blood work.

A patient with both diabetes and pancreatic cancer requires additional assessment so therapy can be selected based on careful consideration of the patient's glycemic state. Oral hypoglycemic agents (OHAs) are reviewed to determine whether the patient's renal or hepatic status precludes the use of the medication. Metformin or sulfonlyureas should be substituted with another medication if renal insufficiency or significant hepatic impairment are present.

Pancreatic insufficiency from surgery and tumor cause abdominal pain, bloating, and diarrhea, particularly after eating. Pancreatic insufficiency is the syndrome that results from a deficiency in pancreatic enzymes that are required to properly digest food. This also is a syndrome associated with T1DM and T2DM (Hardt & Ewald, 2011). Gastrointestinal issues such as nausea, anorexia, and diarrhea from pancreatic insufficiency will affect glycemic control and, therefore, medications should be

adjusted with each of these symptoms so that hypoglycemia can be avoided.

Chemotherapy, including an appropriate antiemetic regimen, can increase the risk of hyperglycemia as shown in the case study. Chemotherapy and supportive medications prepared in dextrose and glucocorticoids certainly affect glycemic state. Baseline blood glucose and close monitoring is required even if the patient is not a known diabetic. The comorbid conditions of pancreatic cancer and T2DM require two sets of interdependent goals, oncologic and glycemic control. Both sets of goals are determined primarily by life expectancy. Glycemic goals will be more liberal if the patient has an incurable cancer; oncologic goals will focus on prolonging quality of life. If the patient has a curable circumstance, glycemic goals will be much tighter so that microvascular and macrovascular complications are minimized during and after cancer treatment. Other factors that affect glycemic goals include patient motivation, risks associated with hypoglycemia, duration of T2DM, other comorbidities, presence of vascular complications, and presence of adequate family and financial support (Ismail-Beigi et al., 2011).

Interventions

No evidence-based studies are available to guide diabetic management in curative and palliative oncology settings. Metformin as first OHA therapy is the only evidence-based recommendation in the general T2DM population. Second- and third-tier therapies are based on provider preferences and general trends. Interventions must be extrapolated from established guidelines and recommendations in palliative care literature. General guidelines for the management of T2DM were published in a position statement from the American Diabetes Association and the European Association for the Study of Diabetes (Inzucchi et al., 2012). The guidelines apply to patients receiving curative cancer therapy with a long life expectancy. Individualization of diabetes therapy will depend on type of chemotherapy or other modality and its impact on T2DM, but the goal of effectively reducing HbA1c and blood glucose define therapy.

Implications for Nursing Practice

In the case study, oncologic goals were determined to be palliation, symptom control, and maximizing quality of life. Although glycemic goals were relaxed (blood glucose level below 200 mg/dl), significant hyperglycemia occurred, which affected quality of life. Table 1 lists the various medications used to treat T2DM and highlights points that pertain to patients with cancer.

D.N. was taking metformin and glimepiride, but glycemic control was lost once he initiated therapy with dextrose-based medications and steroid antiemetics. That led to severe hyperglycemia, which can cause a nonketotic hyperosmolar state (NKHS) or, less often, diabetic ketoacidosis (DKA). These conditions are life threatening and require immediate and intense interventions. NKHS has a mortality rate of about 40%, whereas DKA is less than 10% (Merck & Co., Inc., 2010–2011). Both conditions cause polyuria, polydipsia, mental status changes, tachycardia, and hypotension. The endocrinologist changed therapy to metformin with short-acting insulin based on blood glucose levels that were monitored three times daily.

Glucocorticoids not only increase hepatic glucose production, but also increase insulin resistance. In fact, this may continue after they are stopped (Childs, Cypress, & Spollett, 2005). Insulin requirements may be higher during glucocorticoid treatment, and close glucose monitoring is needed to adjust OHA and insulin doses down after discontinuing steroids. In continuous dosing of steroids for a set time

Table 1. Common Oral Hypoglycemic Agents

Drug Class	Drug Name	Mechanism of Action	Special Considerations for Patients With Cancer
Biguanides	Metformin	Decreases hepatic glucose production	Contraindicated in renal or significant hepatic impairment Gastrointestinal side effects Must be discontinued 24 hours before and 48 hours after IV contrast for computed tomography scan because of combined nephrotoxicity. Serum creatinine should be checked prior to restarting metformin.
Dipeptidyl peptidase-4 inhibitors	Sitagliptin, saxagliptin, and linagliptin	Increases insulin secretion and decreases glucagon secretion	Safe in renal insufficiency Low drug-to-drug interactions Possible pancreatitis
Glucagon-like peptide-1 receptor agonists	Exenatide bydureon and liraglutide	Increases insulin secretion and decreases glucagon secretion. Slows gastric emptying	Gastrointestinal side effects Possible pancreatitis
Metglitinides	Repaglinide and nateglinide	Increases insulin secretion	Short acting with frequent dosing and dosing flexibility Risk of hypoglycemia
Sulfonylureas	Glimerperide and glipizide	Increases insulin secretion	Contraindicated in renal or significant hepatic impairment Increased risk of hypoglycemia when used in combination with another oral hypoglycemic agent
Thiazolidinediones	Pioglitazone and rosiglitazone	Increases insulin sensitivity	Edema and/or congestive heart failure Bone fractures

Note. Based on information from Inzucchi et al., 2012; Singer, 2007.

Clinical Highlights: Pancreatic Cancer and Diabetes Mellitus

Definition

In 2012, 43,920 new cases of pancreatic cancer will be diagnosed with 37,390 deaths—making pancreatic cancer the fourth leading cause of cancer-related death in the United States (Howlader et al., 2011). About 80% of patients with pancreatic cancer have either diabetes mellitus or impaired glucose metabolism (Permert et al., 1994). Most patients are diagnosed with advanced disease and face the challenge of managing diabetes while receiving treatment for pancreatic cancer. In addition, the complications of hyperglycemia and hypoglycemia can cause side effects of confusion, altered mental state, polydipsia, and polyuria and lead to unnecessary hospitalizations. Evidence has shown that better glycemic control results in decreased morbidity, mortality, and length of stay (Garg, Bhutani, Alyea, & Pendergrass, 2007).

Glycemic Control

The degree of glycemic control is primarily dictated by life expectancy. A pancreatectomy is a curative surgery but will induce type 1 diabetes (absence of insulin) and pancreatic insufficiency. Patients are insulin dependent and use pancreatic enzyme replacement to maintain adequate nutrition. Blood glucose for these patients is very labile, not only from the lack of insulin, but also from decreased glucagon production which disrupts gluconeogenesis. A distal or partial pancreatectomy may require some degree of supplementation with pancreatic enzymes and either an oral hypoglycemic agent or insulin. Patients with a hemoglobulin A1c (HbA1c) greater than 6% postoperatively will most likely require insulin therapy. Various treatment approaches can be used, such as intermediate basal insulin with administration of prandial (mealtime) short-acting insulin or premixed insulin that has long- and short-acting insulin combined in one preparation (Dintzis & Golden, 2011). For these patients, recommendations are for tighter glycemic control using 2012 guidelines from the American Diabetes Association and the European Association for the Study of Diabetes (Inzucchi et al., 2012). This includes HbA1c less than 7%, fasting and pre-meal glucose less than 130 mg/dl, and postprandial glucose less than 180 mg/dl (Inzucchi et al., 2012).

Advanced or unresectable pancreatic cancer presents a different set of goals. Depending on life expectancy, less restrictive glycemic controls are recommended. HbA1c levels of 7%–8.3% are more realistic, with a pre-meal glucose of less than 200 mg/dl recommended. Glycemic control remains an important issue in these patients because quality of life is a priority. Oral medication is preferred, but insulin may be required during certain situations such as use of glucocorticoids, severe physical or emotional stress, or significant infection.

End-of-life care requires adjustment of diabetes medications depending on degree of hepatic and renal impairment, oral intake, and life expectancy. The goal is prevention of hypoglycemia, avoidance of hyperglycemia symptoms (i.e., polydipsia, polyuria, and change in mentation), and minimization of invasive procedures such as blood glucose monitoring and injecting insulin (King et al., 2012). Although no evidence-based guidelines are available, short-acting insulin given twice daily with blood glucose monitoring has been suggested by some palliative care practitioners (Ford-Dunn, Smith, & Quinn, 2006). If life expectancy is short, blood glucose monitoring may be discontinued.

Complications of Therapy

Complications from diabetic therapy can result from either too stringent or too lax control of blood glucose. Avoidance of hypoglycemia is a priority in patients with cancer and diabetes. The challenge is maintaining glycemic control in the face of other issues associated with pancreatic cancer, such as pancreatic insufficiency, nausea, anorexia, and diarrhea, and treatment-related effects such as the use of steroids as antiemetics and chemotherapy-induced nausea and vomiting. Hypoglycemia can induce cardiac arrhythmias and falls in older adults, and is more common in patients receiving insulin (Inzucchi et al., 2012).

Severe hyperglycemia (blood glucose greater than 500 mg/dl) can induce diabetic ketoacidosis or nonketotic hyperosmolar state. Both syndromes are life threatening and require intensive interventions of insulin and electrolyte and fluid replacement. Often, insulin infusions and intensive care admission is necessary to provide the level of care required. Nursing education of the patient and family regarding the symptoms associated with both hypo- and hyperglycemia and directions on when to seek immediate medical care are essential.

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- Patients should be screened for diabetes prior to starting oncologic therapy (i.e., fasting blood glucose or hemoglobin A1c).
- Patients with pancreatic cancer may have altered glucose metabolism.
- Patients with diabetes have increased risk of infection, electrolyte abnormalities, vascular events, renal insufficiency, and neuropathy.
- Baseline blood glucose and close monitoring is required for any patient starting on glucocorticoids, chemotherapy that impairs glucose metabolism, or treatment regimens that require a dextrose-based vehicle for delivery.
- Patients who take metformin need to stop the medication 24 hours before and 48 hours after IV contrast for computed tomography scans. Renal function should be reassessed prior to reinitiating metformin.
- Pancreatic insufficiency or other gastrointestinal issues will impact blood glucose control and put a patient at risk for hypoglycemia.
- Patients should be provided with education about proper nutrition and eating patterns, blood glucose monitoring, and prevention, identification, and treatment of hyperglycemia and hypoglycemia.
- A collaborative relationship should be established with the diabetes care provider and an action plan should be developed to treat the patient's diabetes during cancer therapy. The drug regimen should be reinforced with the patient and family members.

Figure 1. Recommendations for Nursing Management of the Patient With Diabetes and Pancreatic Cancer

Note. Based on information from Leak et al., 2009.

period, long-acting insulin is required to provide a basal dose of insulin and, depending on blood glucose levels, short-acting soluble insulin may be added to the regimen (Singer, 2007). Patients who already are on insulin will require an adjustment and continued close monitoring to further titrate insulin levels. When steroids are administered on an intermittent basis, short-acting insulin based on preprandial glucose levels with adjustment of OHA dosing

is more practical and less complex (King et al., 2012). This plan is established with the assistance of the endocrinologist or primary care physician.

Oncology nurses should assess patients' knowledge and ability to control blood glucose through monitoring blood glucose, injecting insulin, and dietary and exercise regimens. Injections and blood glucose monitoring often can overwhelm patients with cancer and their family, and the risk of hypoglycemia is significant. Nutritional status directly affects the glycemic control. Pancreatic insufficiency requires aggressive intervention to maintain adequate nutrition and stable blood glucose. A clinical dietitian referral is appropriate for assessment and recommendation regarding pancreatic enzymes. Close monitoring and adjustments are required to establish the proper dosing of replacement enzymes. The patient in the case study gained better glycemic control once the pancreatic enzyme replacement was stabilized and his weight stabilized. Figure 1 lists key points for oncology nurses to consider when caring for these patients.

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