In Brief

Diabetes and cancer are two diagnoses that individually overwhelm both patients and clinicians. Approximately 8–18% of people with cancer have diabetes. Together, these two diseases can pose formidable challenges to clinicians caring for this difficult patient population. Unfortunately, our knowledge of this topic is limited by insufficient evidence to determine how best to manage diabetes while simultaneously treating cancer. This article seeks to review some of the most common problems encountered by clinicians caring for these patients.

Clinical Challenges in Caring for Patients With Diabetes and Cancer

Helen M. Psarakis, RN, APRN

Diabetes and cancer are two diagnoses that individually overwhelm both patients and clinicians. Approximately 8–18% of people with cancer have diabetes.[1] Together, these two diseases can pose formidable challenges to clinicians caring for this difficult patient population. Unfortunately, our knowledge of this topic is limited by insufficient evidence to determine how best to manage diabetes while simultaneously treating cancer. This article seeks to review some of the most common problems encountered by clinicians caring for these patients.

Cancer Screening and Prevention

Several studies published within the past decade demonstrate that patients with a chronic disease are less likely to receive preventive services, such as cancer screenings, than their counterparts without diabetes.[2–5] A recent retrospective study addressed cancer screening in patients with diabetes.[6] After examining the mammography rates of 69,168 Canadian women with diabetes and 663,519 Canadian women without diabetes, the authors concluded that patients with complex chronic diseases are 32% less likely to receive this routine cancer screening, even though they see primary care and specialty physicians more frequently than their counterparts without diabetes. The discrepancy could not be explained by differences in comorbidity, income, age, access to care, or use of estrogen therapy. Instead, it was attributed to time constraints during office visits for complex chronic disease care, perceptions of decreased life expectancy by both patients and health care providers, and sociocultural barriers to health education. This should serve as a reminder for clinicians to question patients about their primary health care as routinely as they are screened for diabetes complications.

This trend of decreased prevention services is disturbing given the evidence to suggest that insulin resistance and diabetes are linked to higher incidences of some cancers. Researchers hypothesize that exposure to hyperglycemia, elevated insulin concentrations, and the growth-promoting effects of IFG-I may stimulate the development or progression of cancer. People with type 2 diabetes are at higher risk for developing breast, pancreatic, liver, kidney, endometrial, and colon cancers. Patients with type 1 diabetes are more likely to develop cervical and stomach cancers.

Several studies have also demonstrated that patients with diabetes and cancer have a poorer prognosis compared with those without diabetes. Diabetes and hyperglycemia are associated with higher infection rates,

shorter remission periods, and shorter median survival times, as well as higher mortality rates.[7–10]

Cancer Treatment

Chemotherapeutic Agents

Patients with diabetes may present unique challenges to clinicians making cancer treatment decisions. Patients with long-standing diabetes or a history of poorly controlled diabetes may present for cancer treatment with preexisting renal, cardiac, or neuropathic complications. Several chemotherapeutic agents are known to cause or exacerbate these conditions. For example, cisplatin is known to cause renal insufficiency, and the anthracyclines may cause cardiotoxicity. Cisplatin, paclitaxel, and vincristine may be neurotoxic. Unfortunately, many of these side effects from chemotherapeutic agents are permanent.

Successful cancer treatment usually requires at least 85% of the chemo-therapeutic dose be given. Patients with diabetes must be carefully monitored before initiation of and during chemotherapy. Treatment decisions must be based on the patient's clinical picture, but always with the knowledge that any alterations in dose, timing of administration, or substitution of an alternate chemotherapeutic agent may compromise outcomes by lowering the treatment response rate and shortening survival.[10]

Glucocorticoids

The use of glucocorticoids in patients with pre-existing diabetes typically wreaks havoc on postprandial glycemic control. Unfortunately, glucocorticoids are routinely used in many cancer treatment protocols. Glucocorticoid treatment for cancer patients usually consists of short-term therapy at a high dose. Lower-dose steroids are also used to prevent chemotherapy-induced nausea and vomiting. All patients should be screened for diabetes before initiating glucocorticoid therapy and routinely monitored thereafter. These medications raise blood glucose through increased insulin resistance, gluconeogenesis, glycogenolysis, and decreased insulin production and secretion.[11]

It is also common for patients to be diagnosed with diabetes while receiving glucocorticoid therapy. Family history of diabetes, a personal history of gestational diabetes, increased age, obesity, and high doses of steroids are the strongest predictors for glucocorticoid-induced diabetes.[12]

Treatment of hyperglycemia resulting from glucocorticoids depends on the type of diabetes, severity of the elevated blood glucose levels, and dose and duration of the therapy. Giving steroids in multiple doses throughout the day instead of a single bolus dose or administering the total daily steroid dose intravenously over 24 hours can assist in controlling hyperglycemia. Patients with preexisting diabetes may be kept on their oral hypoglycemic agents and monitored carefully. However, these agents are usually inadequate for managing hyperglycemia in this setting. Patients using insulin before glucocorticoid therapy will typically require both basal and preprandial insulins. These patients may require two to three times their usual dose(s) of insulin. Insulin is the preferred drug for managing steroid-induced or exacerbated hyperglycemia in patients with known diabetes. Many patients will require basal and prandial bolus insulins to attain adequate glycemic control.[12–14]

Insulin doses may be estimated based on the patient's weight and administered subcutaneously. Use of an intravenous insulin infusion is another quick way to lower blood glucose as well as estimate the total daily insulin requirement in insulin naive patients. However, many hospitals are resistant to using intravenous insulin drips outside of the intensive care setting because of fear of hypoglycemia. Hourly glucose monitoring and insulin drip rate titrations place an added burden on the nursing staff. Regardless of the route or setting, insulin doses should be titrated daily as needed and should be tapered as glucocorticoid therapy is tapered to avoid hypoglycemia.[11–17]

Tube Feeding and Total Parenteral Nutrition

Tube feeding and total parenteral nutrition (TPN) are frequently used in oncology to supplement or replace a regular diet for patients who cannot sustain their usual intake of nutritional requirements. Hyperglycemia is a frequent complication from both of these forms of nutrition. It may be exacerbated by coexisting infection, the use of steroids, and the physiological response to the stress of severe illness. Hyperglycemia can lead to dehydration, diabetic ketoacidosis (DKA), or hyperosmolar hyperglycemic state (HHS) if left untreated.

Adding regular insulin to the TPN solution can help control blood glucose levels. Initial doses are usually 1 unit per 10 g of carbohydrate. The dose should be titrated daily until glycemic control is attained. Using a lower carbohydrate formula will help with glycemic control in enterally fed patients.

These patients may also benefit from the use of basal insulin. The type of basal insulin used depends on the duration of the tube feeding. Some clinicians prefer glargine for continuous tube feeding. However, NPH or detemir given 2–3 times per day may work as well and allow for a quicker titration of the insulin dose. The University of Vermont is successfully using a protocol of 70/30 (NPH/regular) given every 8 hours. The starting dose calculation varies based on renal/hepatic/cardiac dysfunction, obesity, open wounds/infection, or steroid therapy. NPH and the NPH/regular 70/30 mix also offer an easier transition from continuous to timed or bolus tube feeding because a dose can be eliminated when the feedings are discontinued. Patients receiving tube feeding or TPN should have their blood glucose monitored every 4–6 hours. Short- or rapid-acting insulin dosed according to an algorithm may be given every 6 hours to correct for any hyperglycemia.[18–20] Hypoglycemia is likely to occur if TPN is stopped abruptly. Gradually decreasing the infusion rate at least 1 hour before discontinuing TPN reduces the risk of hypoglycemia.[20]

Nausea and Vomiting

Nausea and vomiting are common adverse drug reactions in some chemotherapy regimens. These reactions can occur in anticipation of therapy, acutely during or within 24 hours of the therapy, or may persist over an extended period of time after therapy. Breakthrough nausea and vomiting may occur, despite prophylactic treatment.

All patients should be screened for a history of nausea and vomiting before initiation of any chemotherapy. The history should include nausea and vomiting related to motion sickness, anesthesia, pregnancy, and any previous chemotherapy treatments. It should also include the frequency, severity, and duration of episodes, as well as the effect of nausea and vomit-

ing on the patient's ability to eat and drink. Document all previous treatments for nausea and vomiting, including medications, doses, frequency, and effectiveness of the therapy.

Always consider the differential diagnoses for nausea and vomiting. These diagnoses include but are not limited to metabolic abnormalities (including DKA and HHS), bowel obstruction, infection, hepatic dysfunction, increased intracranial pressure, medication interactions, and radiation therapy.

Before initiating any chemotherapy regimen, consider the emetogenic potential of any agent or combination of agents in conjunction with the patient's history of nausea and vomiting and pretreat the patient accordingly. Tables 1 and 2, created by Yale New Haven Hospital's Oncology Nursing and Pharmacology Services, rank chemotherapy agents in order of those most likely to induce emesis in adult and pediatric patients along with the appropriate antiemetic treatment.

Patients with diabetes should be assessed frequently for nausea and vomiting, hydration status, ability to eat and drink, and level of glycemic control. Encourage patients to eat small, frequent meals, avoiding sweet, fatty, salty, or spicy foods that may increase the severity of nausea and vomiting. Treat any breakthrough nausea. Consider increasing the frequency of blood glucose monitoring for any patient with nausea and vomiting or a decreased tolerance to food and

Table 1. Yale New Haven Hospital Guidelines for the Control of Chemotherapy-Induced Emesis in Adult Patients

Emetogenic Level	Frequency of Emesis	Chemotherapy Agent	Antiemetic Dose and Schedule
5	> 90%	Carmustine > 250 mg/m^2 Cisplatin ≥ 50 mg/m^2 Cyclophosphamide > 1,500 mg/m^2 Dacarbazine Dactinomcin Mechlorethamine Streptozocin Any agent used at myeloablative doses	Ondansetron, 8 mg i.v. + Dexamethasone 20 mg i.v., pretreatment + At 8–12 hours after treatment or at bedtime, give: Prochlorperaxine, 10 mg i.v./orally *or* Metoclopramide, 20–40 mg i.v./orally Lorazepam 0.5–1 mg i.v./orally may be given pre- or posttreatment if needed
4	60–90%	Carboplatin Carmustine ≤ 250 mg/m^2 Cisplatin < 50 mg/m^2 Cychlophosphamide > 750–1,500 mg/m^2 Cytarabine > 1 g/m^2 Doxorubicin > 60 mg/m^2 Ifosfamide > 1,000 mg/m^2 Irinotecan Melphalan i.v. Methotrexate > 1,000 mg/m^2 Oxaliplatin Procarbazine (orally)[a]	Ondansetron 8 mg i.v. + Dexamethasone 20 mg i.v., pretreatment + At 8–12 hours after treatment or at bedtime, give: Prochlorperaxine 10 mg i.v./orally *or* Metoclopramide 20-40 mg i.v./orally Lorazepam 0.5–1 mg i.v./orally may be given pre- or posttreatment if needed
3	30–60%	Cyclophosphamide ≤ 750 mg/m^2 Cyclophosphamide orally[a] Doxorubicin 20–60 mg/m^2 Epirubicin ≤ 90 mg/m^2 Gemcitabine Hexamethylmelamine orally[a] Idarubicin Ifosfamide ≤ 1000 mg/m^2 Lomustine orally[b] Methotrexate 250–1,000 mg/m^2 Mitoxantrone	Ondansetron 8 mg i.v., pretreatment + Dexamethasone 10–20 mg i.v., pretreatment
2	10–30%	Docetaxel Etoposide 5-Fluorouracil < 1,000 mg/m^2 Liposomal doxorubicin Methotrexate > 50–249 mg/m^2 Mitomycin Paclitaxel Teniposide Thiotepa Topotecan	Dexamethasone 4–8 mg i.v./orally, pretreatment

Continued on page 160

Table 1. Yale New Haven Hospital Guidelines for the Control of Chemotherapy-Induced Emesis in Adult Patients, cont'd

Emetogenic Level	Frequency of Emesis	Chemotherapy Agent	Antiemetic Dose and Schedule
1	< 10%	Asparaginase Bleomycin Busulfan orally Chlorambucil orally 2-Chlorodeoxyadenosine Fludarabine Hydroxyurea Methotrexate ≤ 50 mg/m^2 Melphalan orally 6-Mercaptopurine Tamoxifen 6-Thioguanine Vinblastine Vincristine Vinorelbine	No routine pretreatment recommended

[a]The most highly emetogenic agent in the combination should be identified, and the contribution of other agents should be considered by using the following rules: *1*) level 1 agents do not contribute to the emetogenicity of a given regimen; *2*) adding one or more level 2 agents increases the emetogenicity of the combination by one level greater than the most emetogenic agent in the combination; *3*) adding level 3 and level 4 agents increases the emetogenicity of the combination by one level per agent.

[b]Oral chemotherapeutic agents that are highly emetogenic at high doses and may be less emetogenic in lower doses given over a longer period (i.e., 2 weeks). Oral procarbazine and cyclophosphamide are usually given in combination chemotherapy regimens that include a moderate dose of corticosteroid (prednisone), which can serve as a sufficient antiemetic. On the other hand, the combination of moderate-risk emetogenic drugs can result in high emetogenic potential and should be treated accordingly. Although given orally, lomustine is highly emetogenic and should be treated with the listed premedication.

Reprinted from Yale New Haven Hospital: Nausea and vomiting related to cancer chemotherapy. In *Clinical Practice Manual*. New Haven, Conn., Yale New Haven Hospital, 2005

drink, especially if a steroid is used to manage emesis.

Adjust antihyperglycemic medication doses accordingly. Consider using a short-acting secretagogue (nateglinide or repaglinide) instead of a sulfonylurea (glimepiride, glipizide, glyburide) for postprandial glycemic control. Advantages include dosing intervals that can be timed with meals or held when patients are unable or unwilling to eat. Nateglinide and repaglinide are also much quicker to peak and have a shorter half-life than the sulfonylureas (Table 3). Rapid-acting insulins, such as aspart, glulisine, and lispro, have similar advantages as the nonsulfonylurea secretagogues but can also be dosed immediately after a meal. Rapid-acting insulin is also easier to titrate to precisely cover the amount of carbohydrate consumed during meals, thus affording patients more flexibility in food selections and quantity.

Blood Glucose Management During End-of-Life Care

Glycemic control goals may become less stringent but should not be ignored during end-of-life care. Some patients may desire tight glycemic control as a means of exerting some degree of control over an otherwise untenable situation. Insulin and oral hypoglycemic agents should still be used in "comfort care" or "palliative care" patients because the signs and symptoms of uncontrolled hyperglycemia decrease quality of life. A blood glucose goal of < 200 mg/dl minimizes the risk of polyuria, polydipsia, electrolyte imbalance, and dehydration and may be a realistic goal for some patients. Clinicians should elicit patients' opinions and adhere to their wishes when making treatment decisions. These decisions should be reevaluated and revised with each significant change in patients' clinical picture and always within the context of the patients' overall goals.

Conclusion

Overall, the treatment of and therapies for diabetes in the setting of cancer present a major challenge for clinicians. Maintaining adequate glucose control reduces the incidence of infection in at-risk patients with cancer. Sustaining adequate nutrition and providing appropriate calories for patients receiving chemotherapy demands careful glucose control with whatever therapy improves the clinical situation. Having an understanding of the complexities of both diseases is necessary to achieve the best outcome.

References

[1]Ko C, Chaudhry S: The need for a multidisciplinary approach to cancer care. *J Surg Res* 105:53–57, 2002

[2]Beckman T, Cuddihy R, Scheitel S, Naessens J, Killian J, Pankratz V: Screening mammogram utilization in women with diabetes. *Diabetes Care* 24:2049–2053, 2001

[3]Kief C, Funkhouser E, Fouad M, May D: Chronic disease as a barrier to breast and cervical cancer screening. *J Gen Intern Med* 13:357–365, 1998

[4]Fontana S, Baumann L, Helberg C, Love R: The delivery of preventive services in primary care practices according to chronic disease status. *Am J Public Health* 87:1190–1196, 1997

[5]Redelmeier D, Tan S, Booth G: The treatment of unrelated disorders in patients with chronic medical diseases. *N Eng J Med* 338:1516–1520, 1998

[6]Lipscombe L, Hux J, Booth G: Reduced screening mammography among women with diabetes. *Arch Intern Med* 165:2090–2095, 2005

[7]Bloomgarden Z: Diabetes and cancer. *Diabetes Care* 24:780–781, 2001

[8]Bloomgarden Z: Second World Congress on the Insulin Resistance Syndrome: mediators, pediatric insulin resistance, the polycystic ovary syndrome, and malignancy. *Diabetes Care* 28:1821–1830, 2005

[9]Balkau B, Kahn H, Courbon D, Eschwege E, Ducimetiere P: Hyperinsulinemia predicts fatal liver cancer but is inversely associated with fatal cancer at some other sites. *Diabetes Care* 24:843–849, 2001

Table 2. Yale New Haven Hospital Guidelines for the Control of Chemotherapy-Induced Emesis in Pediatric Patients

Emetogenic Level	Frequency of Emesis	Chemotherapy Agent	Antiemetic Dose and Schedule
High	> 90%	Busulfan intravenously Carmustine Cisplatin > 75 mg/m^2 Cisplatin < 75 mg/m^2* Cyclophosphamide ≥ 1,250 mg/m^2 Dacarbazine ≥ 500 mg/m^2 Ifosfamide/Carboplatin or Cisplatin/Etoposide (ICE) Lomustine > 60 mg/m^2 Melphalan intravenously Methotrexate ≥ 10,000 mg/m^2 Mitoxantrone > 15 mg/m^2 Any agent used at myeloablative doses	Ondansetron, 0.15 mg/kg i.v./orally 30 minutes pre-chemotherapy, then every 4 hours for 2 additional doses. (alternatively, ondansetron, 0.45 mg/kg 30 minutes pre-chemotherapy for one dose daily) + Dexamethasone, 8 mg/m^2 i.v./orally pre-chemotherapy, then 4 mg/m^2 i.v./orally every 6 hours Repeat on each day of chemotherapy *Consider ondansetron as above plus dexamethasone pre-chemotherapy only For breakthrough nausea and vomiting, consider the following agents: Diphenhydramine 0.5 mg/kg i.v. (may increase to 1 mg/kg, to a maximum 50 mg/dose) + Promethazine, 0.5 mg/kg i.v. (maximum 25 mg/dose) every 6 hours as needed *or* Chlorpromazine, 0.55 mg/kg i.v./orally (maximum 40 mg/dose), may repeat every 4–6 hours *or* Lorazepam, 0.05 mg/kg i.v. (maximum 3 mg/dose), may repeat every 8–12 hours *or* Dexamethasone, 5–10 mg/m^2 i.v./orally, may repeat every 12 hours as needed If one or more of these agents fails, consider a single dose of ondansetron, 0.15 mg/kg i.v. For delayed nausea and vomiting associated with cisplatin or cyclophosphamide, consider treatment with one of the following 12–24 hours postchemotherapy: chlorpromazine, lorazepam, or ondansetron
Moderate	30–60%	Carboplatin Cyclophosphamide i.v. < 1,250 mg/m^2 Cytarabine ≥ 1 g/m^2 Dactinomycin Daunorubicin Doxorubicin Idarubicin Ifosfamide Methotrexate 250–10,000 mg/m^2 Mitoxantrone ≤ 15 mg/m^2	Ondansetron, 0.15 mg/kg i.v./orally 30 minutes pre-chemotherapy, then every 4 hours for 2 additional doses (alternatively, ondansetron, 0.45 mg/kg 30 minutes pre-chemotherapy for one dose daily) Add as needed dexamethasone (8 mg/m^2) prechemotherapy, then 4 mg/m^2 every 6 hours if ondansetron alone fails
Low	10–30%	Cytarabine < 1 g/m^2 Etoposide Fluorouacil < 1,000 mg/m^2 Paclitaxel Teniposide Topotecan	Dexamethasone, 5–10 mg/m^2 i.v./orally prechemotherapy *or* Ondansetron, 0.15 mg/kg i.v./orally prechemotherapy
Very Low	< 10%	Asparaginase Bleomycin Cladribine Corticosteroids Cyclophosphamide orally Hydroxyurea Mercaptopurine Methotrexate ≤ 250 mg/m^2 Thioguanine orally Vinblastine Vincristine	No antiemetic prophylaxis necessary

*In multiple agent regimens, the most highly emetogenic agent should be identified.
Very low level (< 10%) agents do not contribute to emetogenicity of combination regimens.
Adding one or more low-level (10–30%) agent(s) increases emetoginicity of the combination by one level more than the most emetogenic agent.

Reprinted from Yale New Haven Hospital: Nausea and vomiting related to cancer chemotherapy. In *Clinical Practice Manual.* New Haven, Conn., Yale New Haven Hospital, 2005

Table 3. Comparison of Sulfonylureas and Nonsulfonylurea Secretagogues*

Agent	Dose (mg)	Dose Interval	Peak (hours)	Half-life (hours)	Duration (hours)
Glyburide	2.5, 5	Daily, twice daily	4	10	12–24
Micronized gyburide	1.5, 3, 6	Daily, twice daily	2	4	12–24
Glipizide	5, 10	Daily, twice daily	1–3	2–4	12–24
Glipizide-GITS	2.5, 5, 10	Daily	6–12	N/A	24
Glimepiride	1, 2, 4	Daily	2–3	9	24
Nateglinide	60, 120	Three times daily with meals	0.3	1	4
Repaglinide	0.5, 1, 2	Three or four times daily with meals	1	1	4–6

*Adapted from Inzucchi SE: *Diabetes Facts and Guidelines 2006*. New Haven, CT: Yale University School of Medicine, 2006

[10]Richardson L, Pollack L: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol* 2:48–53, 2005

[11]Childs B, Cypress M, Spollett G (Eds.): *Complete Nurse's Guide to Diabetes Care*. Alexandria, Va., American Diabetes Association, 2005, p. 320

[12]Clement S, Braithwaite SS, Magee M, Ahmann A, Smith EP, Schafer RG, Hirsch IB: Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 27:553–591, 2004

[13]Volgi J, Baldwin D: Glucocorticoid therapy and diabetes management. *Nurs Clin North Am* 36:333–339, 2001

[14]Childs B, Cypress M, Spollett G (Eds.) *Complete Nurse's Guide to Diabetes Care*. Alexandria, Va., American Diabetes Association, 2005, p. 320–322

[15]Hirsch I, Braithwaite S, Verderese C: *Practical Management of Inpatient Hyperglycemia*. Lakeville, CT, Hilliard Publishing, 2005, p. 30

[16]Trence D: Management of patients on chronic glucocorticoid therapy: an endocrine perspective. *Prim Care Clin Office Pract* 30:593–605, 2003

[17]Braithwaite S, Barr W, Rahman A, Quddusi S: Managing diabetes during glucocorticoid therapy. *Post Grad Med* 104:163–166, 1998

[18]Leahy J: Insulin management of diabetic patients on general medical and surgical floors. In *Improving Inpatient Diabetes Care: A Call to Action Conference*. Washington, D.C., 2006. p. 145–149

[19]Lyman B: Metabolic complications associated with parenteral nutrition. *J Infusion Nurs* 25:36–44, 2002

[20]McMahon M, Rizza R: Concise review for primary-care physicians: nutrition support in hospitalized patients with diabetes mellitus. *Mayo Clin Proc* 71:587–594, 1996

Helen M. Psarakis, RN, APRN, is a diabetes clinical nurse specialist at Yale New Haven Hospital in New Haven, Conn.