Hyperglycemic-Inducing Neoadjuvant Agents Used in Treatment of Solid Tumors: A Review of the Literature

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Purpose/Objectives: To review the literature regarding the development of hyperglycemia associated with neoadjuvant agents used in the treatment of solid tumor cancers.

Data Sources: Research articles were obtained from PubMed, CINAHL®, and Cochrane Reviews. The following search terms were used alone and in combination: diabetes, glycemic control, chemotherapy, androgen deprivation therapy, interferon-alpha, immunosuppressants, cancer, neoplasms, and hyperglycemia.

Data Synthesis: Twenty-two studies were identified reporting the development of hyperglycemic events in patients who received a variety of chemotherapeutic agents.

Conclusions: Findings suggest patients are at risk for the development of hyperglycemia from certain chemotherapeutic agents. Docetaxel, everolimus, and temsirolimus alone or in combination with other agents can promote hyperglycemia. Androgen-deprivation therapy commonly used in prostate cancer, increases the risk for the development of hyperglycemia and diabetes.

Implications for Nursing: Oncology nurses play an important role in the identification and treatment of hyperglycemia in patients receiving chemotherapy. Future research is needed that focuses on the association between glycemic control and adverse outcomes in patients with a solid tumor cancer who are at risk for treatment-induced hyperglycemia.

Key Words: neoplasm; chemotherapy; hyperglycemia

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Patients with a solid tumor cancer are at risk for hyperglycemia (blood glucose > 126 mg/dL) during treatments. Hyperglycemia can contribute to the risk for adverse outcomes such as infections and nonmalignancy-related mortality (Ali et al., 2007; Fuji et al., 2007; Hammer et al., 2009; Storey & Von Ah, 2012). In addition, hyperglycemia may increase the risk for development of clinical toxicities, grade 4 neutropenia, neutropenic fever, sepsis, and neuropathy (Brunello, Kapoor, & Extermann, 2011). Hyperglycemia during cancer treatment is one of the clinical toxicities that can cause chemotherapy dose delays or reductions (Brunello et al., 2001; Richardson & Pollack, 2005). Hyperglycemia may decrease the response to chemotherapeutic agents (Zeng et al., 2010). Understanding the contributors to hyperglycemia in patients with a solid tumor cancer is essential to create interventions for improved outcomes.

In patients with a solid tumor cancer, many factors can contribute to hyperglycemia, including nutritional imbalances (Jenkins et al., 2002; Martin-Salces, de Paz, Canales, Mesejo, & Hernandez-Navarro, 2008), physical inactivity (Katz, 2007; Moien-Afshari et al., 2008), older age (Stookey, Pieper, & Cohen, 2004), high body mass index (Roumen, Blaak, & Corpeleijn, 2009), high stress levels (Godbout & Glaser, 2006), and infections (Turina, Christ-Crain, & Polk, 2006). These factors are also associated with the development of type 2 diabetes (T2D). Having preexisting T2D (the hallmark of which is hyperglycemia) is one factor that increases the risk for hyperglycemic events during cancer treatment (Fuji et al., 2007). About 18% of all individuals with cancer have preexisting diabetes at the time of diagnosis (Barone et al., 2008).

Patients do not have to have preexisting diabetes to encounter glycemic problems and related adverse outcomes while undergoing treatment for cancer. The current prevalence of hyperglycemia among patients with a solid tumor cancer with and without preexisting diabetes is currently unknown. One study that investigated allogeneic hematopoietic cell transplantation recipients found an overall median blood glucose of 133 mg/dl (hyperglycemic) among 1,175 patients, and blood glucose at a level greater than 200 mg/dl was related to an almost twofold increased risk for mortality compared to a level of 101–150 mg/dl ($p = 0.0009$) (Hammer et al., 2009). This population hinted at the potentially larger glycemic issue for all patients with

cancer. Evaluating the many contributors to hyperglycemic events, both in isolation and in combination, can lend greater insights about glycemic events and how to best mitigate them. The evaluation of single factors is an important first step.

Treatment-induced hyperglycemia may result from medications used in the management of symptoms and side effects associated with chemotherapy. Corticosteroids, in particular, are commonly used and are known to induce hyperglycemia (Leak, Davis, Houchin, & Mabrey, 2009; Psarakis, 2006). Independent of corticosteroids, the specific impact of chemotherapeutic agents, as a contributor to hyperglycemia, is not fully understood, yet is essential for glycemic management. By increasing the current knowledge of how chemotherapeutic agents may impact glycemic levels, interventions targeted toward better management of individuals at risk for hyperglycemic events during treatment can be developed.

The purpose of this integrative review is to explore the specific chemotherapeutic agents that can increase the risk for hyperglycemia and to discuss the related clinical implications among adults with solid tumor cancers. The specific aims are to identify chemotherapeutic agents that contribute to hyperglycemia in adults with solid tumor cancers and discuss implications for nursing practice and future research to mitigate hyperglycemic events in adults with solid tumor cancers receiving hyperglycemic-inducing chemotherapeutic agents.

Methods

Articles were retrieved for review through a combination of computer and manual searches of selected hyperglycemia and cancer-related abstracts and publications. The reference lists of included papers were checked for additional relevant studies. A review of the literature was conducted using a search of PubMed and CINAHL®. The review covered publications from 2000–2012. The following search and MeSH terms were used alone and in combination: *hyperglycemic* or *glycemic control*, *chemotherapy*, *androgen deprivation therapy*, *interferon-alpha*, *immunosuppressant*, and *cancer* or *neoplasm*. The inclusion criteria included English-language articles, literature reviews, meta-analysis, research publications, and studies conducted with human participants. Glucocorticoids are a known hyperglycemic-inducing agent; therefore, studies that exclusively evaluated glucorticoids with hyperglycemic events were excluded. Editorials, case studies, and unpublished dissertations were also excluded.

Articles were reviewed initially by abstracts and titles, yielding 183 abstracts. Four duplicate articles were excluded, as were abstracts that did not meet the inclusion criteria. A total of 179 full-text articles were obtained for review, as well as 8 additional articles that were found by hand searches. Abstract and full-paper appraisal resulted in the exclusion of 165 of these articles, leaving 22 relevant papers. These 22 included 12 papers related to chemotherapy, 7 to androgen-deprivation therapy (ADT), and 3 interferon-alpha (INF-α) studies.

Results

A number of chemotherapeutic regimens administered for the treatment of various solid tumors were evaluated for hyperglycemic-inducing properties (see Table 1). Malignant tissues secrete enzymes, cytokines, chemokines, and other factors that help the malignancy to thrive; some of these are inflammatory (Grivennikov & Karin, 2011; Mantovani, Allavena, Sica, & Balkwill, 2008) and may contribute to hyperglycemic states (Moretti, Bennett, Tornatore, Thotakura, & Franzoso, 2012). Research is limited related to differences in inflammatory-provoking properties by tumor site; however, to mitigate the possibility of such variances, the authors cross-evaluated the studies by tumor site to procure a more accurate evaluation of the therapies believed to induce hyperglycemia. Findings were variable with evaluations by both agent administered and tumor site.

Tumor Site

Prostate: Eight studies focused on patients with prostate cancer, including seven studies with patients who received ADT (Basaria, 2008; Basaria, Muller, Carducci, Egan, & Dobs, 2006; Braga-Basaria et al., 2006; Derweesh et al., 2007; Hakimian et al., 2008; Inaba et al., 2005; Ribeiro, Camara, Segre, Srougi, & Serrano, 2010) and one study of patients who received docetaxel with or without high-dose calcitriol and who were ADT independent (Beer et al., 2007). Three of the ADT articles were reviews, and all had similar findings (Basaria, 2008; Hakimian et al., 2008; Ribeiro et al., 2010). ADT was associated with an increased risk for altered body composition (Basaria, 2008), metabolic complications including insulin resistance and hyperglycemia (Basaria, 2008; Hakimian et al., 2008), T2D (Hakimian et al., 2008), metabolic syndrome and dyslipidemia (Hakimian et al., 2008; Ribeiro et al., 2010), metabolic syndrome secondary to hypogonadism (Ribeiro et al., 2010), osteoporosis (Hakimian et al., 2008), cardiovascular disease (Basaria, 2008; Hakimian et al., 2008; Ribeiro et al., 2010), and mortality from cardiovascular disease (Basaria, 2008). Similarly, a cross-sectional study found 55% of men who received long-term ADT experienced metabolic syndrome (Braga-Basaria et al., 2006), whereas another cross-sectional study found increased insulin resistance and hyperglycemia also

Table 1. Studies of Neoadjuvant Agents and Effects on Glycemic Control

Study	Design and Sample	Measurement	Outcomes
Basaria, 2008	Literature review regarding complications of ADT	Not reported	ADT increases risk for decrease muscle mass, which may result in decreased glucose uptake and lead to insulin resistance and diabetes. Insulin resistance may develop within a few months of starting ADT.
Basaria et al., 2006	Cross-sectional study with 53 men without a history of DM;18 men had prostate cancer and had received ADT for at least 12 months prior to the onset of the study, 17 were age-matched men with nonmetastatic prostate cancer who did not receive ADT, and 18 were age-matched controls.	Total and free testosterone levels, serum insulin, leptin levels, and homeostatic model assessment for insulin resistance	Serum total and free testosterone were significant ($p < 0.0001$) in the ADT group when compared to the other groups. Men in the ADT group had significantly ($p < 0.01$) higher BMIs, glucose levels, insulin levels, leptin levels, and homeostatic model assessments for insulin resistance.
Baselga et al., 2012	Double-blind phase III randomized trial comparing everolimus and exemestane to exemestane and placebo with 724 patients with hormone receptor–positive advanced breast cancer with recurrence or progression	Progression-free survival, overall survival, overall response rate, clinical benefit rate, time to deterioration of ECOG performance status, safety, and quality of life **Efficacy and safety assessments:** CT or MRI of chest, abdomen, and pelvis at baseline and every six weeks until disease progression; bone scan or skeletal survey six weeks before randomization; hematologic function, biochemical measurements, and vital signs assessed at baseline and at each visit; and AEs graded according to the NCI CTCAE, version 3.0	Serious AEs occurred in 23% of patients in the combination therapy group and 12% in the exemestane-alone group. The most common grade 3 and 4 events were stomatitis (8% in combination group and 1% in exemestane-alone group), anemia (6% and 1%, respectively), dyspnea (4% and 1%, respectively), hyperglycemia (4% and less than 1%, respectively), fatigue (4% and 1%, respectively), and pneumonitis (3% and 0%, respectively).
Beer et al., 2007	Double-blind randomized phase II trial to evaluate the efficacy and safety of calcitrol (DN-101) plus weekly docetaxel compared with placebo plus weekly docetaxel in 250 men with metastatic adenocarcinoma of the prostate with evidence of progression	Physical examination, assessment of AEs including skeletal-related events, and concomitant medications, urinalysis, and serum PSA every 4 weeks; body weight, hematology profile, and chemistry profile weekly	No increase in toxicity when DN-101 was added to docetaxel. Incidence of grade 3 or 4 toxicities was 70% in patients given placebos and 58% in patients treated with DN-101. The most common grade 3 and 4 clinical toxicities were fatigue (16% placebo, 85% DN-101), infection (13% placebo, 8% DN-101), and hyperglycemia (12% placebo, 6% DN-101).
Bellmunt et al., 2008	Phase III trial comparing temsirolimus alone or temsirolimus plus interferon-alpha with interferon-alpha alone in 616 patients with advanced renal cell carcinoma, no prior systemic therapy, and three or more of six poor risk factors	**Baseline measurements:** Complete blood count, serum cholesterol, triglyceride levels, and renal and hepatic function Blood counts, serum chemistries, vital signs, and AEs based on the NCI CTCAE, version 3.0, assessed weekly	The most common drug-related grade 3 or 4 toxicities in patients receiving temsirolimus were anemia (13%) and hyperglycemia (9%). Temsirolimus was associated with metabolic AEs of high serum glucose, triglycerides, and cholesterol.

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ADT—androgen deprivation therapy; AE—adverse event; BMI—body mass index; CT—computed tomography; CTCAE—Common Terminology Criteria for Adverse Events; DM—diabetes mellitus; ECOG—Eastern Cooperative Oncology Group; FPG—fasting plasma glucose; 5-FU—5-fluorouracil; HbA1c—glycated hemoglobin; MRI—magnetic resonance imaging; NCI—National Cancer Institute; PSA—prostate-specific antigen; WHO—World Health Organization

Table 1. Studies of Neoadjuvant Agents and Effects on Glycemic Control *(Continued)*

Study	Design and Sample	Measurement	Outcomes
Bex et al., 2005	Phase II trial of pegylated interferon alpha-2b with 22 patients with metastatic renal cell carcinoma with removal of the primary tumor	Toxicities were graded using the NCI CTCAE. Monitoring of toxicities occurred every two weeks and included physical examination, hematology, biochemistry, and patient history with a focus on constitutional symptoms.	The most common clinical toxicities were fatigue, sweating, and headache. Fatigue was the most common grade 3 or 4 toxicity. One patient experienced grade 4 hyperglycemia. No cases of grade 1–3 hyperglycemia were reported.
Braga-Basaria et al., 2006	Cross-sectional study to determine the association between hypogonadism and metabolic syndrome with 58 men with prostate cancer, 20 men with prostate cancer undergoing ADT, 18 age-matched men with nonmetastatic prostate cancer who had received local treatment and had an increasing PSA, and 20 age-matched men with normal PSA levels	Metabolic syndrome defined as the presence of three of five of the following criteria: fasting plasma glucose level more than 110 mg/dl, serum triglyceride level 150 mg/dl or greater, serum high-density lipoprotein level less than 40 mg/dl, waist circumference more than 102 cm, and blood pressure of 130/85 mmHg or greater	55% of the men in the ADT group met criteria for metabolic syndrome compared to 22% and 20% in the other groups. The presence of hyperglycemia was significantly higher ($p = 0.006$) in the ADT group.
Derweesh et al., 2007	Retrospective study to investigate incidence of new onset diabetes and worsening glycemic control in patients with DM after receiving ADT with 396 patients undergoing ADT for prostate cancer	Variables included BMI, pretreatment serum PSA level, Gleason grade, clinical stage, type of ADT, ADT schedule (continuous versus intermittent), receipt of vitamin D or bisphosphonate therapy, and HbA1c and fasting blood glucose levels.	113 individuals with diabetes were identified, 77 patients had DM prior to starting ADT, 319 patients did not have evidence of diabetes prior to ADT, and 36 patients who identified as not having diabetes developed diabetes during treatment. 10% of the 77 patients with preexisting diabetes had a mean rise in HbA1c of 10% or greater.
Feliu et al., 2001	Phase II trial to assess the response rate and survival obtained with a sequential regimen of chemotherapy. Chemotherapy consisted of weekly paclitaxel 150 mg/m^2 x 6, followed two weeks later by cisplatin 100 mg/m^2 on day 1, gemcitabine 1,000 mg/m^2 on days 1 and 14, and vinorelbine 25 mg/m^2 on days 1 and 14.	Followed WHO guidelines for treatment response and toxicity	Hyperglycemia was present in 12 patients, 4 of whom had levels greater than 250 mg/dl. Dexamethasone 20 mg was given one hour prior to administration of paclitaxel. Authors attributed hyperglycemia to dexamethasone.
Feng et al., 2012	Retrospective study to analyze the prevalence and characteristics of secondary diabetes induced by 5-FU chemotherapy with 422 patients with colorectal cancer who received 5-FU–based chemotherapy	AEs were classified according to the CTCAE, version 4.0, and were documented daily during chemotherapy period. FPG levels and prechemotherapy laboratory workup was completed before starting each chemotherapy cycle and at 3 and 6 months after the final cycle. Individuals who had abnormal FPG levels, oral glucose tolerance test, plasma C-peptide, and insulin were collected. Data on the use of diabetes therapy (diet control or use of oral drugs or insulin) and discontinuation of chemotherapy were obtained.	42 patients developed diabetes during chemotherapy or after the completion of the last chemotherapy. Grade 3 and 4 AEs related to hyperglycemia occurred in 7 patients despite antidiabetic therapy. Diabetes-related AEs had an impact on chemotherapy administration in six patients; four had to stop chemotherapy because of grade 3 and 4 peripheral neuropathy, two patients required a change in their chemotherapy regimen, and diabetes-related death occurred in three patients.

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Table 1. Studies of Neoadjuvant Agents and Effects on Glycemic Control *(Continued)*

Study	Design and Sample	Measurement	Outcomes
Fury et al., 2012	Phase I open-label, single-institution trial of daily everolimus plus low-dose weekly cisplatin with 36 adults aged 18 years or older with advanced solid tumors	Toxicity assessed with the NCI CTCAE, version 3.0. Dose-limiting toxicity was defined as grade 4 febrile neutropenia, neutropenia for seven or more days, other grade 4 hematologic toxicity, or any other grade 3 or 4 nonhematologic treatment toxicity (excluding nausea, vomiting, rash, untreated hyperlipidemia, diarrhea for less than 48 hours, fatigue for fewer than 7 days, or any toxicity requiring treatment delay for greater than 7 days). Laboratory data included complete blood count, comprehensive metabolic panel, and magnesium, collected at each scheduled clinic visit.	The most common AEs were fatigue, low hemoglobin, and elevated glucose. 23 individuals experienced grade 1–4 hyperglycemia, and 3 experienced grade 3 or 4 hyperglycemia. For most individuals, hyperglycemia was mild and did not appear to be exacerbated by dexamethasone that was given weekly.
Galanis et al., 2005	Phase II trial of temsirolimus in recurrent glioblastoma multiform with 65 adults aged 18 years older with histologic confirmation of a grade 4 astrocytoma at primary diagnosis or recurrence	NCI CTCAE, version 2.0, was used to grade toxicities. Complete blood counts were obtained weekly. Chemistry groups were performed at baseline and before each cycle. Neuroimaging included head MRI or CT with contrast at baseline and before third cycle and every second cycle afterward.	28 patients required dose reduction because of toxicity. Grade 3 hematologic toxicity occurred in 11% of the patients; the most common hematologic toxicity was thrombocytopenia (9%). Grade 3 or higher nonhematologic toxicity occurred in 51% of patients; the most common were toxicities were hypercholesterolemia (11%), hypertriglyceridemia (8%), hyperglycemia (8%), rash (8%), and fatigue (6%).
Hakimian et al., 2008	Literature review	Used MEDLINE® to identify English-language literature from 1950 until the present using key words of *hypogonadism, testosterone, androgen deprivation therapy, hormonal treatment, prostate cancer, diabetes, metabolic syndrome,* and *cardiovascular disease*.	Men receiving ADT had an increased risk for developing insulin resistance, hyperglycemia, and diabetes as a result of induced hypogonadism.
Hudes et al., 2007	Multicenter phase III trial of temsirolimus, interferon-alpha, or both for advanced renal cell carcinoma with 626 patients with previously untreated poor prognosis of metastatic renal cell carcinoma	Baseline laboratory tests included complete blood count, serum cholesterol, triglycerides, and renal and hepatic function. Serum chemical analyses and blood counts were monitored weekly or biweekly with monitoring of AEs. Toxicity was measured with the NCI CTCAE, version 3.0.	Asthenia was the most common AE in the two groups receiving interferon (26% interferon group and 28% in the combination group; 11% of patients in temsirolimus group reported grade 3–4 asthenia). Hyperglycemia, hypercholesterolemia, and hyperlipidemia were common in the combination group. Hyperglycemia of any grade occurred in 11 patients in the interferon group, 26 in the temsirolimus group, and 17 in the combination group. Grade 3 or 4 hyperglycemia occurred in 2 patients in the interferon group, 11 in the temsirolimus group, and 6 in the combination group.

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Table 1. Studies of Neoadjuvant Agents and Effects on Glycemic Control *(Continued)*

Study	Design and Sample	Measurement	Outcomes
Inaba et al., 2005	Case-control study with 2 men with hyperglycemia and 144 men with normal glucose tolerance	Pancreatic β-cell function and insulin sensitivity were estimated by calculation from fasting plasma glucose and serum insulin using the homeostatic model assessment method.	Both cases of men with hyperglycemia, one with and one without known diabetes, demonstrated that ADT increased the development of hyperglycemia and reduced insulin sensitivity and pancreatic β-cell function when compared to the control group.
Infante et al., 2009	Phase II nonrandomized, combination trial of weekly docetaxel, vinorelbine, and trastuzumab with 61 patients with HER2- positive metastatic breast cancer	History and physical; complete blood count; chemistry profile; chest x-ray; CT of chest, abdomen, and pelvis; and electrocardiography were performed prior to the beginning of therapy. Cardiac ejection fraction by multigated acquisition scan was determined at baseline and every 12 weeks while receiving trastuzumab. Toxicity was graded according to the NCI CTCAE, version 3.0.	The most common hematologic toxicity was neutropenia (72%). Other grade 3 and 4 toxicities included fatigue (12%), pain (10%), myalgia (7%), hyperglycemia (7%), and stomatitis (5%).
Lee et al., 2004	Prospective phase II clinical trial of docetaxel and cisplatin as primary chemotherapy for treatment of locally advanced breast cancer with 57 women aged 18 years or older with clinically palpable T3 and T4 breast tumors	Primary tumor size was recorded at three-week intervals. Pretreatment evaluation included complete blood count, routine chemistries and liver function tests, chest x-ray, bone scans, and electrocardiography. Toxicity was determined using WHO recommendations.	The most common grade 3 and 4 toxicities in the primary docetaxel and cisplatin group were hyperglycemia (n = 6, 11%), leukopenia (n = 3, 5%), and infection (n = 3, 5%). Hyperglycemia was one of the most common grade 1 or 2 toxicities (n = 18, 32%). The most common toxicities in the adjuvant doxorubicin and cyclophosphamide group were leukopenia (n = 7, 12%), infection (n = 4, 7%), and neuropathy (n = 3, 5%).
Lim et al., 2011	Prospective, single-center, open-label phase I trial of capecitabine plus everolimus with 15 patients with advanced unresectable or metastatic gastric adenocarcinoma	Toxicities and AEs were evaluated using NCI CTCAE, version 3.0, and were assessed weekly and evaluated until 21 days after the last dose.	Grade 3 hyperglycemia occurred in one patient.
Naing et al., 2011	Phase I trial of cixutumumab combined with temsirolimus with 42 individuals with advanced cancer	Toxicities were measured using NCI CTCAE, version 3.0. Vital signs were measured prior to each infusion. Hematology, blood chemistries, urinalysis, and physical examinations were regularly performed.	The most common treatment-related toxicities were hyperglycemia (grade 3 or greater = 4.8%), hypertriglyceridemia grade 3 or greater = 2.4%), hypercholesterolemia (grade 3 or greater = 2.4%), thrombocytopenia (grade 3 or greater = 4.8%), and mucositis (grade 3 or greater = 2.4%). 57% of patients in the study experienced some level of hyperglycemia.
Okabe et al., 2002	Prospective study to investigate the usefulness and AEs of cisplatin, 5-FU, and dl-leucovorin with 16 patients with advanced colorectal cancer	Toxicities were assessed using the WHO criteria.	The most common toxicities were neurotoxicity (100%), diarrhea (92%), stomatitis and rash (85%), and nephrotoxicity and hyperglycemia (77%). Grade 3 or 4 hyperglycemia occurred in two patients.

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Table 1. Studies of Neoadjuvant Agents and Effects on Glycemic Control (*Continued*)

Study	Design and Sample	Measurement	Outcomes
Ribeiro et al., 2010	Literature review	Literature review used MEDLINE for literature published from 1966 to June 2009 using the key words of *androgen deprivation therapy, androgen suppression therapy, hormone treatment, prostate cancer, metabolic syndrome,* and *cardiovascular disease*	Identified increase in incidence of insulin resistance and glycemia, as well as diabetes in patients who underwent ADT
Spigel et al., 2010	Phase I/II trial of preoperative oxaliplatin, docetaxel, and capecitabine with concurrent radiation therapy with 59 patients with stage I–III adenocarcinoma or squamous cell carcinoma of the mid or distal esophagus or gastroesophageal junction	Toxicities were assessed using the NCI CTCAE, version 3.0.	The most common grade 3–4 nonhematologic toxicities were anorexia (20%), dehydration (16%), diarrhea (8%), dysphagia (10%), esophagitis (20%), fatigue (12%), hyperglycemia (6%), nausea (16%), pulmonary symptoms (14%), sepsis (6%), and vomiting (16%).

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after long-term ADT use (Basaria et al., 2006). A retrospective cohort study found a risk for diabetes in all patients who receive ADT, independent of preexisting diabetes (Derweesh et al., 2007). A case-control study took a different approach with the assumption that hyperglycemia was going to occur in patients receiving ADT and found a return to normal blood glucose using insulin therapy followed by thiazolidinedione (Inaba et al., 2005). The one non-ADT study that targeted patients with prostate cancer found lower incidence of hyperglycemia among patients who received docetaxel with high-dose calcitriol (20%) compared to those who received docetaxel plus placebo (26%) (Beer et al., 2007).

Breast: Four studies showed outcomes of hyperglycemia in women with breast cancer caused by treatments (Baselga et al., 2012; Infante et al., 2009; Lee et al., 2004; Naing et al., 2011). Two studies included docetaxel (Infante et al., 2009; Lee et al., 2004) but in combination with other chemotherapies. In a two-arm study in which all patients received dexamethasone as a premedication, hyperglycemia occurred in 43% who received docetaxel plus cisplatin compared to hyperglycemia in 9% of patients who received doxorubicin plus cyclosphosphamide (Lee et al., 2004). In a study that assessed all patients with HER2-positive breast cancer who received dexamethasone prior to weekly docetaxel, vinorelbine, and trastuzumab, 7% incurred grade 3-4 hyperglycemia (Infante et al., 2009). Everolimus was administered to postmenopausal patients with hormone-receptor–positive advanced breast cancer with an outcome of 4% incurring grade 3 or 4 hyperglycemia compared to 1% in a placebo group (Baselga et al., 2012). A study by Naing et al. (2011) evaluated cixutumumab with temsirolimus in patients with a variety of advanced cancers, including breast cancer. Two of the 42 patients in the study had known preexisting diabetes and incurred grade 3 hyperglycemia, which was a dose-limiting factor. However, whether these two patients had breast cancer is unknown; the type of cancer associated with hyperglycemia was not reported. Hyperglycemic incidence varied from 1%–43%, including intervention.

Renal cell carcinoma: Three studies investigated INF-α for the treatment of advanced or metastatic renal cell carcinoma and included hyperglycemia as an outcome measure (Bellmunt, Szczylik, Feingold, Strahs, & Berkenblit, 2008; Bex et al., 2005; Hudes et al., 2007). A phase II study of pegylated INF-α found fatigue and hyperglycemia as toxic effects from treatment, with 55% unable to complete treatment because of the toxicities; fatigue was experienced more often than hyperglycemia (Bex et al., 2005). Two studies compared INF-α to temsirolimus for the treatment of advanced or metastatic renal cell carcinoma (Bellmunt et al., 2008; Hudes et al., 2007); temsirolimus was associated with higher rates of hyperglycemia compared to INF-α. Bellmunt et

al. (2008) conducted a randomized, controlled trial and found higher rates of hyperglycemia, anemia, and other adverse outcomes in the temsirolimus group compared to the INF-α group. Hudes et al. (2007) evaluated three goups (temsirolimus, INF-α, or both) and found equal adverse outcomes of hyperglycemia. Hyperglycemia was noted as an adverse outcome in all of these studies; however, quantification of the hyperglycemic events is lacking.

Colorectal: Two studies targeted patients with advanced colorectal cancer (Feng et al., 2012; Okabe et al., 2002). The study by Naing et al. (2011) also included patients with colorectal cancer but did not distinguish outcomes based on diagnosis (hyperglycemia outcome discussed in the breast cancer section). Feng et al. (2012) retrospectively evaluated patients with colorectal cancer who received 5-fluorouracil (5-FU) who did not have preexisting diabetes and found that 23% developed hyperglycemia during treatment. Among the 363 patients in the study, 14 had received glucocorticoids; however, they concluded that post-steroid diabetes in these patients was not directly related to the steroid dose (Feng et al., 2012). In a small prospective study in which all patients received methylprednisone prior to the administration of cisplatin as part of a combination of PFL therapy (cisplatin, 5-FU, and leucovorine) for unresectable or recurrent colorectal carcinoma, 23% of patients experienced grade 2–4 hyperglycemia (Okabe et al., 2002). Less than 25% of patients in the Feng et al. (2012) and the Okabe et al. (2002) studies experienced hyperglycemic events.

Esophageal and gastric: A study by Spigel et al. (2010) evaluated preoperative oxaliplatin, docetaxel, and capecitabine (ODC) with radiation therapy for localized carcinoma of the esophagus or gastroesophagus. All patients received dexamethasone as a premedication to the ODC, and 6% experienced hyperglycemic states categorized as grade 3 hyperglycemia. Lim et al. (2011) administered capecitabine and everolimus to patients with refractory metastatic gastric cancer with two patients experiencing grade 3 hyperglycemia. Both of these studies found few hyperglycemic events.

Lung: Two studies included patients with lung cancer (Feliu et al., 2001; Fury et al., 2012), although the types of tumors were histologically different. Patients received daily everolimus plus weekly low-dose cisplatin (preceded by dexamethasone). The patients had advanced cancer, including pulmonary carcinoid tumor. Eighty-two percent were found to have experienced hyperglycemic events, with 11% incurring grade 3 or greater hyperglycemia (Fury et al., 2012). Paclitaxil with dexamethasone as a premedication followed by cisplatin-gemcitabine-vinorelbine was administered to patients with advanced non-small cell lung cancer with 24% incurring hyperglycemia (Feliu et al., 2001). The authors felt the hyperglycemia was exclusively steroid-related (Feliu et al., 2001). These studies showed widely varied outcomes.

Glioblastoma multiforme: Temsirolimus with diphenhydramine as a premedication was administered to 65 patients with recurrent glioblastoma multiforme, among whom 8% experienced hyperglycemia (Galanis et al., 2005). Hyperglycemia was implicated as a contributor to grade 3 or greater nonhematologic toxicity found in 51% of patients (Galanis et al., 2005).

The study by Fury et al. (2012) discussed in the lung cancer section also included patients with head and neck and thyroid cancers, and one to two patients each with different diagnoses including endometrial, basal cell, adenoid cystic carcinomas, and other cancer sites. A majority (82%) of the patients experienced hyperglycemia (Fury et al., 2012). The risk of hyperglycemia could not be attributed to specific cancer sites.

Treatment

Docetaxel was administered in combination regimens with vinorelbine and trastuzumab (Infante et al., 2009), cisplatin (Lee et al., 2004), calcitriol (Beer et al., 2007), or oxaliplatin with or without capecitabine (Spigel et al., 2010). Dexamethasone was given to patients in three of these studies (Infante et al., 2009; Lee et al., 2004; Spigel et al., 2010) and was undisclosed in the other docetaxel studies. Grade 3 or 4 hyperglycemia ranged from 6% (Beer et al., 2007; Spigel et al., 2010) to 15% (Lee et al., 2004). Overall, 43% of patients who received docetaxel and cisplatin were hyperglycemic (Lee et al., 2004). Because of the varying combinations of chemotherapeutic agents administered with docetaxel, hyperglycemic findings cannot be attributed to docetaxel alone.

Everolimus was also not administered as an independent agent. Studies included everolimus with cisplatin (Fury et al., 2012), exemestane, exemestane without everolimus (Baselga et al., 2012), or capecitabine (Lim et al., 2011). Glucocorticoid administration was not disclosed except in the Fury et al. (2012) study in which weekly doses of dexamethasone were given. In this study, hyperglycemic events at all grades occurred in 82% of patients (Fury et al., 2012). Grade 3 hyperglycemia was found in all studies and ranged from 4%–11%. Only the study by Baselga et al. (2012) demonstrated a difference in hyperglycemic events (grade 3–4) with everolimus at 4% compared to 1% in the control group that did not receive this therapy.

Temsirolimus was given alone (Galanis et al., 2005) or with cixutumumab (Naing et al., 2011). Eight percent of patients became hyperglycemic (grade ≥ 3) with temsirolimus alone (glucocorticoids not administered) (Galanis et al., 2005). In comparison, hyperglycemia was the most prevalent metabolic complication in patients who

received temsirolimus with cixutumumab with 4.8% at a grade ≥ 3 (glucocorticoid use unknown) (Naing et al., 2011). It is difficult to distinguish between temsirolimus with and without cixutumumab as hyperglycemic-inducing agents between these two studies.

Two studies compared temsirolimus to INF-α (Bellmunt et al., 2008; Hudes et al., 2007). Hudes et al. (2007) evaluated temsirolimus with or without INF-α and INF-α alone. Outcomes of hyperglycemia were found in all groups and were worse in the temsirolimus group alone (Hudes et al., 2007). Bellmunt et al. (2008) similarly compared INF-α with temsirolimus and found worse hyperglycemia.

Three studies included the use of INF-α therapy (Bellmunt et al., 2008; Bex et al., 2005; Hudes et al., 2007). Studies by Bellmunt et al. (2008) and Hudes et al. (2007) also included comparisons with temsirolimus (discussed previously). The study by Bex et al. (2005) found the toxic effects of hyperglycemia and fatigue sequelae to INF-α therapy, with fatigue being a major dose-limiting factor. One of 13 patients in that study experienced grade IV hyperglycemia (Bex et al., 2005). Two studies included 5-FU in their treatment regimens (Feng et al., 2012; Okabe et al., 2002). Almost 23% of patients who received 5-FU alone became hyperglycemic, of which 10% (n = 36) were diagnosed with treatment-related diabetes (Feng et al., 2012). Dexamethasone was administered to 14 of these patients with secondary diabetes, but the diabetes was not attributed to the steroid based on the low dose given (Feng et al., 2012). Methylprednisolone sodium succinate was given to all patients prior to cisplatin administered as part of a combination therapy with 5-FU and leucovorin (Okabe et al., 2002). Grades 2–4 hyperglycemia occurred in 23% of this population (Okabe et al., 2002). Direct comparisons between the studies cannot be made because of the differences in regimens.

The combination of paclitaxel, cisplatin, and gemcitabine was administered as a progressive therapy with dexamethasone given prior to the paclitaxel doses (Feliu et al., 2001). Twenty-four percent became hyperglycemic, with 7% reaching isolated blood glucose levels ≥ 250 mg/dl, attributed to the steroid (Feliu et al., 2001). This was the only study evaluating these therapies.

ADT was evaluated in seven studies (Basaria, 2008; Basaria et al., 2006; Braga-Basaria et al., 2006; Derweesh et al., 2007; Hakimian et al., 2008; Inaba et al., 2005; Ribeiro et al., 2010). In addition to hyperglycemia, adverse outcomes included altered body composition, metabolic syndrome, and cardiovascular complications. As an isolated treatment, ADT appears to induce hyperglycemia.

Discussion

The systematic review of 22 studies supported the hypothesis that certain chemotherapeutic agents are associated with an increase in development of hyperglycemia in solid tumor cancers. Although the findings were not consistent among the studies, the data do not necessarily suggest or support a causal relationship. Therefore, these studies provide preliminary evidence for future longitudinal, prospective studies focusing on the relationship of blood glucose levels and outcomes in individuals with a solid tumor cancer who are receiving chemotherapy.

Most cancers are treated with chemotherapeutic or adjuvant agents alone or in combination with other agents. From the review, certain chemotherapeutic or adjuvant agents had greater negative hyperglycemia outcomes than other agents. ADT, docetaxel, and temsirolimus increase the risk for the development of hyperglycemia when administered alone or in combination with other agents. Hyperglycemia appears to be worse when temsirolimus is administered alone versus being administered with another agent (Hudes et al., 2007). INF-α therapy in combination with other agents or alone was found to increase the risk for the development of hyperglycemia. 5-Fluorouracil, used in the treatment of lymphoma, had mixed results because of differences in treatment regimens. Only one study investigated paclitaxel, cisplatin, and gemcitabine, and results indicated that the agents may increase the risk for the development of hyperglycemia; further research is needed with these agents to determine a causal relationship. Research exploring the effects of ADT, used commonly in the treatment of prostate cancer, supports the association between ADT and the development of hyperglycemia in patients with and without diabetes.

The four most common cancers, prostate, breast, lung, and colorectal, were highlighted in this review. The majority of patients with prostate cancer who received long-term ADT were at an increased risk for altered body composition (Basaria, 2008), metabolic syndrome and dyslipidemia (Hakimian et al., 2008; Ribeiro et al., 2010). For patients with breast and lung cancers, the results had a varied hyperglycemic incidence from low to high. Overall, the incidence of hyperglycemia in patients treated for colorectal cancer is higher than other solid tumors. This may be related to the combination of chemotherapeutic agents used to treat colon cancer; other factors such as cancer stage, lifestyle, body mass index, and preexisting comorbidities may also play a role. Studies have shown patients with diabetes are at greater risk for developing colorectal cancers (Meyerhardt et al., 2003). Other cancers, such as esophageal and gastric, treated with common chemotherapeutic agents (i.e., oxaliplatin, docetaxel, capecitabine, and everolimus) are associated with an increased risk for hyperglycemia.

Limitations

The primary strength of this analysis is the use of several international studies providing a comprehensive

review exploring risk of hyperglycemia associated with chemotherapeutic agents administered for the treatment of solid tumor cancers. Limitations included less attention on hematologic malignancies, hematopoietic cell transplantation recipients, and various other cancers. Evaluating the composite factors contributing to hyperglycemic events during and following treatments for cancer is important. Another limitation to this review is that not all of the studies reported if patients received steroids along with the chemotherapeutic agent. As previously mentioned, corticosteroids are known to impact glycemic levels. Future research in this area needs to include the tracking of steroids and other medications that may impact glycemic levels to fully understand the relationship between chemotherapy and hyperglycemia. Despite these studies showing a moderate to strong association of hyperglycemia with the use of chemotherapeutic or adjuvant agents in certain cancer types, long-term prospective studies with a focus on causation are needed.

Implications for Practice

The findings from this review have important clinical, public health, and research implications for understanding hyperglycemic events in patients with a solid tumor cancer who are receiving chemotherapy. Although this review did not focus on differences between patients with and without preexisting diabetes and associated age-related risks, research with this focus is greatly warranted because the incidence of diabetes increases with age (National Institutes of Health, 2011). The presence of diabetes increases the risk for hyperglycemic events during cancer treatment. With the population of older adults estimated to reach more than 72 million by 2030 (U.S. Department of Health and Human Services, 2013)—a reflection of the aging baby boomer cohort—healthcare providers will encounter individuals with both diabetes and cancer more frequently.

The comorbidity of diabetes in patients with cancer has been associated with higher rates of hospitalizations, complications, and mortality compared to individuals with cancer who do not have preexisting diabetes (Barone et al., 2008; Giovanucci et al., 2010). Informing oncology nurses and healthcare professionals about the impact of chemotherapeutic agents on glycemic control in patients with and without diabetes is essential. The authors have identified specific chemotherapeutic agents that healthcare providers can be cognizant of in terms of hyperglycemic events sequelae to their administration. Clinicians are not just treating the cancer or diabetes but simultaneously treating the patient as a whole. Healthcare providers should want to achieve the best possible outcomes for patients. Further research is needed in this area to more clearly define clinical implications.

Future studies are needed that build on these studies. A focus on the relationship between hyperglycemia and cancer-related outcomes in patients with both diabetes and cancer will be beneficial in the development of care protocols for this population. Care of individuals with cancer and diabetes needs to reflect the collaboration from a varied group of professionals, including nurses, physicians, nurse practitioners, diabetes educators, oncology educators, but most importantly, patients and caregivers must be at the center of this plan of care.

Knowledge Translation

Promote earlier detection of hyperglycemia in patients receiving treatment for a solid tumor cancer.

Influence the development of care protocols for the management of hyperglycemia to improve outcomes for patients with or without diabetes.

Facilitate multidisciplinary collaboration to manage hyperglycemia in patients with a solid tumor cancer.

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