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Original Article

Hyperglycemia crisis in head and neck cancer patients with platinum-based chemotherapy

Chien-Yu Huang [a], Yaoh-Shiang Lin [a,b,c], Yu-Hsi Liu [a], Sheng-Chiao Lin [a], Bor-Hwang Kang [a,b,c,*]

[a] *Department of Otolaryngology, Head and Neck Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC*
[b] *School of Medicine, National Defense Medical Center, Taipei, Taiwan, ROC*
[c] *Department of Otolaryngology, Head and Neck Surgery, Tri-Service General Hospital, Taipei, Taiwan, ROC*

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Abstract

Background: The development of a hyperglycemic crisis in platinum-based chemotherapy-treated head and neck cancer patients, such as hyperosmolar hyperglycemic state (HHS), has been reported. Hyperglycemic crises are associated with a high risk of comorbidity and may delay cancer treatment if not promptly managed.
Methods: This is a retrospective study using cancer registry data from a tertiary medical center. Head and neck cancer patients who had been treated with platinum-based chemotherapy from January 2014 to December 2015 were enrolled for review. Exclusion criteria included patients with a known history of type 2 diabetes mellitus (DM). Characteristics of patients who developed type 2 DM after initiation of chemotherapy were compared with non-DM patients, following which the clinical course of the patients developing a hyperglycemic crisis were reviewed.
Results: A total of 185 patients were enrolled, of which seven patients (3.8%) had developed type 2 DM after initiation of platinum-based chemotherapy. No statistically significant differences in age, body mass index, sex, cancer subsite, cancer stage, or chemotherapy regimen were found when comparing new-onset type 2 DM patients with the rest of the patients. Three patients developed diabetic ketoacidosis, HHS, or impending HHS after initiating chemotherapy treatment. The incidence of hyperglycemic crises was 3 out of 185 (1.6%) in this patient group.
Conclusion: Hyperglycemic crisis after cisplatin may be underestimated and may lead to a life-threatening condition. We suggest regular weekly follow-ups of serum glucose level after platinum-based chemotherapy for early detection of hyperglycemia and prevention of a life-threatening crisis.

Keywords: Diabetic ketoacidosis; Hyperglycemia; Hyperglycemic hyperosmolar nonketotic coma; Platinum; Squamous cell carcinoma

1. Introduction

The incorporation of cisplatin-based (i.e., Cis-diamminedichloroplatinum-based) or carboplatin-based chemotherapy into treatment plans for locally advanced, recurrent, unresectable, or metastatic head and neck cancer has been strongly recommended by the National Comprehensive Cancer Network.[1] However, its side effects include dose-dependent neurotoxicity, severe nausea and vomiting, nephrotoxicity, anemia, and thrombocytopenia, which can lead to new concepts regarding to defining unsuitable head and neck patient populations.[2] Furthermore, strict monitoring protocols for cisplatin-treated patients to prevent cisplatin-related acute or late complications have not been well established yet, which hinders compliance to scheduled chemotherapy when encountering unexpected medical conditions.[3] These factors have compromised the benefits of platinum-based chemotherapy.

Insulin resistance, an abnormal homeostasis in blood glucose control, had been reported in anti-neoplastic medications, including platinum-based agents, 5-Fluorouracil (FU), doxorubicin, and paclitaxel.[4] Few studies have discussed the

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* Corresponding author. Dr. Bor-Hwang Kang, Department of Otolaryngology, Head and Neck Surgery, Kaohsiung Veterans General Hospital, 386, Dazhong 1st Road, Kaohsiung 813, Taiwan, ROC.
E-mail address: bhkang@vghks.gov.tw (B.-H. Kang).

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development of diabetes mellitus (DM) in cisplatin-treated head and neck patients.[5–9] Hyperglycemic crisis is defined as acute metabolic complications of diabetes, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).[10] The main symptoms include polyuria, polydipsia, polyphagia, and dehydration. Common precipitating events include infection, cerebral vascular accident, pancreatitis, acute myocardial infarction, trauma, drug abuse including steroids, thiazides, and sympathomimetic agents, alcohol abuse, discontinued or inadequate use of medication, and newly onset DM. The development of a hyperglycemic crisis, including hyperosmolar coma, in this group of patients was scarce yet life threatening.[11] Although all previous data have reported cases of hyperosmolar coma, development of DKA in these groups of patients have not yet been published.

To enhance patient safety when receiving platinum-based chemotherapy, we conducted a retrospective analysis in a tertiary medical center. A head and neck multidisciplinary team established prevalence of hyperglycemic status and crisis in cisplatin-treated head and neck patients.

2. Methods

From January 2014 to December 25, 2015, newly diagnosed head and neck cancer patients who had been admitted to Kaohsiung Veteran General Hospital and assigned to the head and neck multidisciplinary team for head and neck cancer treatment were enrolled after review of both the cancer registry data and chart review. Exclusion criteria included diagnosis of DM or medication use related to diabetes prior to the start of chemotherapy and patients who had not received cisplatin. Basic demographic data, including sex, age, cancer type, staging, treatment course, and serum chemistry lab data, were all recorded. The regimen of cisplatin therapy included hydration with 1000 cc normal saline containing 20 mEq KCl followed by premedication with 3 mg granisetron ivd, 30 mg metoclopramide ivd, 5 mg chlorpheniramine ivd, and 10 mg dexamethasone ivd. Cisplatin was then dripped over an iv pump for 4 h. Next, 3.84 mg metoclopramide PO was prescribed for use three times a day for postchemotherapy antiemetics. DM was defined according to the American Diabetes Association as random plasma glucose $\geq$200 mg/dL (11.1 mmol/L) and impaired fasting glucose with fasting plasma glucose >126 mg/dL (7 mmol/L) and hemoglobin A1C > 6.5% with classic hyperglycemia symptoms.[12]

All statistical analyses and graphics were performed using SPSS (version 15, SPSS, Inc., Chicago, IL) statistical packages. Continuous variables were analyzed with a one-way ANOVA, and categorical variables were compared by Pearson's Chi-square test or Fisher's exact test. This study was reviewed and approved by the Kaohsiung Veteran General Hospital Institutional Review Board (18-CT1-07(171018-1)).

3. Results

A total of 220 patients were enrolled in the study during the initial screening. Twenty-nine patients were diagnosed with diabetes before starting chemotherapy. Ten patients had not received cisplatin in their chemotherapy regimen, leaving a total of 185 patients eligible for chart review. During follow-up checkups, seven patients (3.8%) had developed type 2 DM after initiation of platinum-based chemotherapy. Three patients, including one nasopharyngeal carcinoma patient, had developed DKA, one nasopharyngeal carcinoma patient had developed HHS, and one oropharyngeal squamous cell carcinoma patient had developed impending HHS after initiating chemotherapy treatment. Therefore, the incidence of hyperglycemic crisis was 3 out of 185 (1.6%) in this patient group. The characteristics of the whole study population and the three hyperglycemic crisis patients are listed in Tables 1 and 2. No statistically significant differences in age, BMI, sex, cancer subsite, and cancer stage and regimen were noted when comparing patients who had developed DM to those who had no evidence of the disease. The onset of hyperglycemia was first observed between 8 and 17 days after the last dose of cisplatin. A family history of type 2 DM was a strong risk factor for developing DM. However, no family history was documented in the three hyperglycemic crisis patients. The clinical courses of the three hyperglycemic crisis patients are described herein (Table 2).

3.1. Case 1

A 47-year-old male patient who denied previous underlying disease had nasal obstruction for months and a 10 cm painless mass in his right neck for 1 year. A nasopharyngeal endoscopy disclosed an exophytic mass and a tissue biopsy revealed undifferentiated nonkeratinizing carcinoma. An image study suggested disease status cT3N3bM0, stage IVB. Induction chemotherapy with 80 mg/m^2 cisplatin plus 5-FU was arranged, and the patient tolerated the first and second courses of chemotherapy well. However, 13 days after the second course

Table 1
Characteristics of study populations.

	Develop DM(n = 7)	No DM(n = 178)	*p*
	58.29 ± 10.7	52.63 (10.25)	0.155
BMI	21.68 ± 3.76	21.37 ± 3.85	0.838
Male	7 (100)	157 (88.2)	0.337
Cancer primary site			0.792
Oral cavity	1 (14.3)	27 (15.2)	
Oropharynx	3 (42.9)	34 (19.1)	
Hypopharynx	0 (0)	33 (18.5)	
Nasopharynx	2 (28.6)	65 (36.5)	
Larynx	0 (0)	9 (5.1)	
Others	1 (14.3)	10 (5.6)	
Stage			0.116
I	0 (0)	1 (0.6)	
II	0 (0)	13 (7.3)	
III	2 (28.6)	38 (21.3)	
IV	5 (71.4)	126 (70.8)	
Regimen			0.327
Cisplatin only	2 (28.6)	111 (62.4)	
PF	4 (57.1)	50 (28.1)	
TPF	1 (14.3)	5 (2.8)	
others	0 (0)	12 (6.7)	

BMI = body mass index; PF = cisplatin, 5-FU; TPF = docetaxel, cisplatin, 5-FU.

Table 2
Characteristics of patients receiving cisplatin who developed hyperglycemia crisis.

Case	1	2	3	
Diagnosis	NPC	NPC	Oropharynx SCC	
Cancer Staging	cT3N3bM0	cT3N2M0	cT2N1M0	
Age	47	57	57	
IFG	No	No	No	
BMI	24.31	21.47	22.02	
Glucose	608	1475	689	mg/dL
Sodium	118	111	135	mmol/dL
Potassium	4.4	3.4	4.3	mmol/dL
Urea nitrogen	24	73	38	mg/dL
Creatine	1.71	2.15	1.79	mg/dL
eGFR	45.6	33.8	41.8	ml/min/1.73
Ketone (serum)	2+	neg.	2+	
Osmolality (serum)	269	343	326	mOsm/L
pH	7.314	7.36	7.379	mmHg
pCO_2	16.8	23.9	23.1	mmHg
Bicarbonate	8.3	13.2	13.3	mmol/L
Chemotherapy	PF	PF	Weekly cisplatin	
Cisplatin Dose	80	80	40	mg/m^2
Cycle completed	2	1	3	
Onset day (after last cisplatin)	13	17	8	days

NPC = nasopharynx carcinoma; SCC = squamous cell carcinoma; IFG = impaired fasting glucose; BMI = body mass index; PF = cisplatin, 5-FU.

of chemotherapy, dyspnea, nausea, vomiting, and polydipsia with blurred vision were noted. The patient came to the emergency room for help where a blood glucose of 608 mg/dL was noted with an arterial blood gas pH of 7.314, pCO_2 of 16.8, HCO_3^- of 8.3, and serum ketone of 2^+. After consultation with the metabolic specialist, DKA criteria were not met due to lack of serum chloride data for calculating the anion gap. At initial presentation, before starting the treatment, DKA was more favored than HHS because the patient had a low serum bicarbonate of 8.3 mmol/L, positive serum/urine ketone (serum = 2^+, urine = 5 mg/dL), serum osmolality of 269 mOsm/L, arterial pH close to <7.30, and clear consciousness.[10] The patient was transferred to the metabolic ward for further management. The acute kidney injury recovered to near normal status, with eGFR improving from 45.6 to 74.4 mL/min/1.73, within 1 day after aggressive hydration to treat DKA. After the acute episodes, insulin therapy was prescribed, and the patient became insulin dependent until the 12-month follow-up.

3.2. Case 2

A 57-year-old male patient had newly diagnosed nasopharyngeal carcinoma cT3N2M0, stage III and received induction chemotherapy with 80 mg/m^2 cisplatin plus 5-FU. After the first course of induction chemotherapy, severe weight loss, disturbed conscious, and general malaise were noted. On examination, blood glucose levels up to 1475 mg/dL were noted with blood gas analysis showing pH of 7.36, HCO_3^- of 13.2 mmol/L, and pCO_2 of 23.9 mmHg. The patient was diagnosed with HHS based on his disturbed conscious, glucose level of >1000 mg/dL, serum osmolality of 343.0 mOsm/L, and negative serum and urine ketone with anion gap of 23.8 mmol/L. After discussion with a metabolic specialist, although an anion gap of 23.8 mmol/L may support the diagnosis of DKA, this possibility was excluded on account of the negative serum and urine ketone profile. Emergent insulin pump therapy with resuscitation was initiated and the patient's condition improved. The acute kidney injury recovered to normal status with eGFR improving from 33.8 to 110.7 mL/min/1.73 within 5 days after aggressive hydration to treat the HHS. The patient was dependent on oral anti-diabetes medication up to the 4-year post-event follow-up.

3.3. Case 3

A 57 year-old male with a history of alcoholic hepatitis, peptic ulcer perforation, and esophageal bleeding had newly onset sustained sore throat over the uvula and soft palate for 2 months. A biopsy determined the patient to have squamous cell carcinoma of the uvula cT2N1M0, stage III. After wide excision of the tumor, concurrent chemoradiotherapy was initiated with 35 fractions of 70 Gy and weekly 40 mg/m^2 cisplatin. Before the fourth round of chemotherapy, the patient had nausea and vomiting with general fatigue at home. When the patient was admitted to our ward for evaluation, blood glucose levels up to 689 mg/dL was noted. Blood gas revealed a pH of 7.379, pCO_2 of 23.1, HCO_3^- of 13.3, serum osmolality of 326 mOsm/L, and serum ketone of 2^+ with ketouria. An acute kidney injury was noted. The anion gap was 15.9, with an expected gap of 9.5, and delta-delta was 1.3. Thus, impending HHS was diagnosed after consultation with a metabolic specialist because the patient was in a clear consciousness level but presented with multiple symptoms and signs compatible with HHS. After intensive care from the metabolic specialist, the hyperglycemia was controlled. The acute kidney injury was recovered to near normal status with eGFR improvement from 41.8 to 77.4 mL/min/1.73 within 5 days after aggressive hydration to treat the hyperglycemic crisis. The patient became oral anti-diabetes medication-dependent up to the 2-year post-event follow-up.

4. Discussion

This study analyzed 185 head and neck cancer patients who had received cisplatin-based chemotherapy and found that 3.8% (7 out of 185) of the patients developed DM and 1.6% (3 out of 185) developed a hyperglycemic crisis. Furthermore, our study recorded a case of DKA that developed after cisplatin chemotherapy for head and neck cancer, which had not been reported before.

The first literature published discussing cisplatin treatment and DM was by Dr. Daniel N. Nan,[6] who reported that 11 out of 202 patients (5%) developed DM during the treatment period, with two cases presenting as hyperosmolar coma (1.0%). Other researchers have sporadically reported four cases of hyperosmolar coma related to cisplatin chemotherapy in head and neck cancer, esophageal cancer, and gallbladder cancer patients.[7−9,11] However, none had reported cisplatin chemotherapy developing into DKA. Ketonemia and

metabolic acidosis were developed in insulin deficiency and increased counter-regulatory hormones, including catecholamines, cortisol, glucagon, and growth hormone. Animal studies have suggested cisplatin induces marked glucose intolerance and abnormal glucagon response.[13−15] *In vitro* studies have demonstrated that the presence of cisplatin influences the configuration of native insulin, which may lead to inactivation of the hormone.[16] A retrospective review of 106 patients with locally advanced head and neck cancer suggested that chemoradiation may produce severe serum glucose metabolism alternation.[7]

Aside from head and neck cancer patients, platinum-based chemotherapy has also been an essential drug for adjuvant therapy in ovarian cancer, lung cancer, cervical cancer, and esophagus cancer treatments.[17,18] Toru Nakano et al. reported a case of a 73-year-old female with esophageal cancer that was treated with cisplatin and 5-FU who suffered from HHS after chemotherapy.[8] Sakakura C et al. reported on a 61-year-old woman without a history of DM who had recurrent gallbladder cancer and was treated with cisplatin. The patient was diagnosed as having HHS 7 days after the first cycle of chemotherapy.[9] A project spanning many subspecialties is needed to obtain precise statistics on the effect of platinum on other types of cancer, including ovarian cancer, lung cancer, and cervical cancer, which is beyond the current scope of this study. The possibility of a disease-specific phenomenon was not clear and further studies are required to provide a more solid conclusion.

Precipitants of DKA, which include iatrogenesis, infection, starvation, and intoxication, were all excluded in the three cases of hyperglycemic crisis in our study cohort. Dexamethasone has been commonly used in chemotherapy regimens, and reports discussing its correlation with hyperglycemia in cancer patients have been published. Harris et al. screened 90 patients who had glucocorticoids administered for brain tumor, lymphoma, and bone marrow transplant treatment regimens and found that 18.9% of patients had DM range hyperglycemia. However, no long-term serum glucose follow-up data after these treatments were presented.[19] Lee et al. reported that 32.5% (26 out of 80) of lymphoma patients developed glucocorticoid-induced diabetes during CHOP chemotherapy and none had acute complications, such as HHS.[20] Although premedication with 10 mg dexamethasone in our study population could account for hyperglycemia, corticosteroid-induced ketone production is rarely seen. Also, dexamethasone-induced hyperglycemic crises were found mostly after prolonged use or in pre-diabetic patients and the hyperglycemia should be reversed after discontinuing use of the medication. However, all three of our cases remained diabetic up to the 1-year follow-up.

Other chemotherapy agents correlating to hyperglycemia or hyperglycemic crisis have been reported. Feng et al. reported on a patient with colorectal cancer who died of DKA that developed after the second cycle of chemotherapy with 5-FU.[21] It was not clear if the regimen was combined with other agents, such as oxaliplatin. Carlos Tavares Bello et al. reported on a previously well-controlled type 2 diabetic colorectal cancer patient who developed DKA after FOLFIRI (FOLinic acid, 5-FU and IRInotecan) chemotherapy.[22] Tamas Hickish et al. studied 39 breast cancer patients and found a statistically significant increase in serum glucose levels among patients who received a higher dose of steroids in combination with docetaxel.[23] Guo et al. reported that the combination of carboplatin and paclitaxel administration could cause transient hyperglycemia in rats.[24]

Although both 5-FU and docetaxel were commonly used in head and neck cancer patients and also in our study population, a direct causative relationship was not possible due to the complexity in different doses, intervals, patient background, and small sample size. However, the only common chemotherapeutical agents in all three of our hyperglycemic crisis patients was cisplatin, which became unneglectable in the role of hyperglycemia when compared with other agents like 5-FU and docetaxel.

Acute kidney injury was noted in all three of our hyperglycemic crisis patients. *In vivo* studies showed injury to renal epithelial cells provoked by inflammation, causing kidney injury and dysfunction. Recovery of renal function usually took a period of 2−4 weeks or did not recover at all.[25] Skinner et al.[26] conducted a prospective cohort study and found cisplatin or carboplatin nephrotoxicity did not change significantly over 10 years. Acute kidney injury accompanied by hyperglycemic crisis was assumed to be related to hypovolemia due to glucose-induced osmotic polyuria, which was transient and characterized by a response to fluid infusion.[27] All three of our hyperglycemic crisis patients recovered to normal renal function, with an eGFR >90, from acute kidney injury within 1−5 days. Therefore, the etiology of the acute kidney injury in all three hyperglycemic crisis patients favored volume depletion over cisplatin nephrotoxicity.

Physiological compensation of acidosis and electrolytes were observed in our DKA case (pH 7.314), indicating a delay in seeking medical attention when DKA started and exposing the patient to a life-threatening condition. Nausea and vomiting, two hallmarks of DKA, could be confused with more common cisplatin complications. Thus, accompanying symptoms of DKA, which included dyspnea, polydipsia, polyuria, and dehydration signs, should be taught to cisplatin-treated patients and family members.

Although we had excluded patients with established diagnosis of type 2 DM from our study, preliminary analysis found that none of the patients developing a hyperglycemic crisis were known to have type 2 DM. Possible mechanisms contributing to this difference may be that the known diabetic patients had routine checkups of blood sugar during each hospitalization examination routine or at home, and the patients, as well as their family, were aware of hyperglycemia symptoms and signs.

The recommended guideline for distinguishing platinum-unsuitable head and neck cancer patients[2] was to establish clinical criteria for high risk cases, including cardiovascular disease such as hypertension, unstable cardiac disease, diabetes, and recurrent pulmonary infections in the comorbidities section. Herein, we suggested a more extensive examination

that included regular blood glucose level monitoring not only to fulfill recommendations made by the guidelines but also to detect newly onset diabetes early and prevent hyperglycemic crisis.

A hyperglycemic crisis after cisplatin may be underestimated and lead to life-threatening conditions. Platinum-based chemotherapy-related hyperglycemic episodes were observed 1−2 weeks after cisplatin infusion. Blood glucose should be monitored weekly after platinum-based chemotherapy for early detection of hyperglycemia and prevention of life-threatening crises.

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