Atrial Flutter Associated with Carboplatin Administration

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Objective: To report a novel case of atrial flutter associated with carboplatin administration and review chemotherapy-related cardiac toxicities, focusing on platinum-containing compounds.

Case Report: A 69-year-old man with extensive small cell lung cancer and asymptomatic cardiovascular and cerebrovascular disease was inconsistently adherent to his medication regimen. While undergoing carboplatin infusion, he developed atrial flutter. He had no other immediate arrhythmogenic causes of atrial flutter and the arrhythmia spontaneously reverted to sinus rhythm after 24 hours. His condition remained stable until he died 8 days later. The cause of death was unknown and the family declined postmortem examination.

Discussion: Although this patient's cardiac history and nonadherence to his medications may have increased his susceptibility to develop atrial arrhythmias, the Naranjo probability scale reveals a possible relationship between atrial flutter and infusion of carboplatin. A literature search revealed other adverse cardiac events due to platinum compounds; however, to our knowledge, this case is the first to describe an association with atrial flutter. A definitive causal link cannot be determined, but this may have been the result of a direct arrhythmogenic effect of treatment or to a novel hypersensitivity reaction. Given the potential deleterious impact of drug-induced arrhythmias, we have reported this case to the Food and Drug Administration as a new adverse effect of carboplatin.

Conclusions: Providers should consider cardiac monitoring during carboplatin infusion in patients with known cardiac disease or at high risk of cardiac complications.

Key Words: antineoplastic agents, arrhythmias, heart disease, neoplasms.

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mg/dL. Thirty minutes prior to this infusion, the patient was given oral allopurinol 300 mg and diphenhydramine 25 mg, and intravenous ondansetron 24 mg, dexamethasone 12 mg, and ranitidine 50 mg. He had not yet received the cycle 2, day 1 etoposide infusion. Administration of adenosine revealed atrial flutter as demonstrated on an electrocardiogram (ECG) (Figure 1).

The patient’s history was significant for hypertension, asymptomatic right pontine cerebral vascular accident, and asymptomatic inferior myocardial infarction. One month before this chemotherapy cycle, he was admitted to the hospital for progressive cachexia, postobstructive pneumonia, and hypertensive urgency. An echocardiogram (ECHO) revealed a left ventricular ejection fraction of 40-45%, normal atrial and ventricular sizes, and a small circumferential hemodynamically insignificant pericardial effusion. Computed tomography (CT) and tumor biopsy revealed SCLC metastases to the brain, liver, peritoneum, skin, kidneys, and adrenal gland. He received whole brain irradiation and tolerated his first cycle of carboplatin (370 mg on day 1 based on an AUC of 5) and etoposide (150 mg on days 1-3 based on a body surface area of 1.5) without complications. Upon discharge, he completed a 3-day course of ondansetron 8 mg twice daily, a 7-day course of allopurinol 300 mg daily, and a prolonged dexamethasone tapering regimen, but he was intermittently adherent to his other medications, including pantoprazole 40 mg daily, ipratropium nebulized therapy 3 times daily, oxycodeone 5 mg as needed, aspirin 81 mg daily, docusate 100 mg daily, and metoprolol 12.5 mg twice daily.

On this admission, vital signs were temperature 36.4 °C, pulse 160 beats/min, blood pressure 100/72 mm Hg, and pulse oximetry of 98% on room air. Results of physical examination were significant for a nondisplaced but bounding point of maximal cardiac impulse; a regular tachycardic rhythm with no murmurs, rubs, or gallops; and flutter waves in the jugular veins 4 cm superior to the clavicle at a 30° incline.

Initial laboratory data (Table 1) included a white blood cell count of 3960 µL, normal hemoglobin and platelet count, sodium 134 mEq/L, and thyroid-stimulating hormone (TSH) 0.24 mIU/L (although testing 1 day later showed TSH and thyroxine of 0.64 mIU/L and 0.84 mIU/L, respectively). There were no other electrolyte abnormalities. Serial cardiac enzyme measurements showed normal levels of creatine kinase and creatine kinase-MB and marginally elevated levels of troponin I (0.12-0.18 ng/mL). A CT scan showed no evidence of pulmonary embolism and the tumor burden had decreased radio graphically when compared to a CT study performed 1 month earlier. However, there was persistent disease, including a left anterior mediastinal mass compressing the left upper lobe bronchus, another mass compromising the left main pulmonary artery, and numerous matted precari nal nodes measuring 4.2 × 2.2 cm in composite. There was no evidence of pericardial or myocardial involvement (Figure 2).

The patient developed worsening tachycardia associated with dizziness and shortness of breath. Adequate rate con-
trol with diltiazem and metoprolol was limited by hypoten-
sion. Prior to any planned intervention, his cardiac rhythm 
spontaneously converted to sinus rhythm within 24 hours 
after carboplatin infusion. Two days later and on subse-
quent clinical visits, he remained in sinus rhythm (Figure 
3). Eight days after discharge, the patient died at home. 
The cause of death was presumed to be a cardiac arrhyth-
mia; however, definitive etiology was not determined since 
the family declined postmortem examination.

Discussion

Oncologic chemotherapeutic agents can lead to adverse 
cardiac events. While drug-induced cardiotoxicity is most 
commonly associated with anthracyclines, other chemothera-
peutics have also been associated with heart failure, arrhyth-
mias, changes in blood pressure, and myocardial ischemia. In 
general, antineoplastic agents have been speculated to 
cause 2 different types of chemotherapy-related cardiac dys-
function (CRCD). Type I CRCD is irreversible, dose-depen-
dent, and classically associated with anthracycline agents. 
Damage probably results from free radical formation with re-
sultant increase in intracellular calcium, myocardial damage, 
and clinical decline in left ventricular ejection fraction. 
Type II CRCD, frequently associated with trastuzumab, is 
thought to be due to inhibition of signaling pathways that 
are involved in sarcomere repair and is considered to be re-
versible. In either case, left ventricular dysfunction occurs, 
commonly associated with sequelae such as congestive heart failure or arrhythmias.

Theoretically, any platinum-containing compound could 
cause oxidative stress via a type I CRCD, resulting in an 
increased downstream risk of hypertension, coronary 
artery disease, or heart failure. Furthermore, animal stud-
ies have shown that carboplatin can induce cardiac my-
ocyte apoptosis and heart failure. CRCD is unlikely to be 
the underlying mechanism of platinum-induced toxicity, 
since there is only a single case report describing a tempo-
rary 1-month cardiomyopathy with associated congestive 
heart failure that occurred after carboplatin administra-
tion. Rather, the limited data on adverse cardiac platinum 
events have shown patients to have myocardial infarction 
directly attributable to coronary vasospasm both during 
cisplatin infusions and during the following months. 
Chronically, accelerated rates of hypertension and major 
cardiovascular events have been documented with cis-
platin-based regimens, with a 1.5-1.9 increase in cardiac 
events compared to the general population. For carbo-
platin, the long-term cardiac effects remain unknown.

Platinum-based compounds, especially cisplatin, have 
also been reported to induce arrhythmias. Commonly, sinus 
bradycardia can occur, which resolves spontaneously upon 
cessation of drug infusion. In addition, there are rare re-
ports of other tachyarrhythmias during cisplatin infusion, 
including atrial fibrillation and supraventricular tachycardias. 
For carboplatin, some reports show an association with atrial 
arrhythmias; however, no studies have documented a rela-
tionship with atrial flutter. However, carboplatin has been 
implicated as a cause of third-degree atrioventricular block 
and has been associated with asymptomatic ventricular ec-
topy when administered to children. The pathophysiology
of carboplatin-induced arrhythmias may be attributed to a reversible direct toxic effect, causing individual sarcomeres to have an unstable membrane, resulting in increased differential depolarization and changes in electrical gradients. In addition, platinum administration can cause changes in electrolyte gradients in the heart by interfering with potassium, calcium, or magnesium homeostasis.\(^3\)

Alternatively, arrhythmias can be a novel manifestation of a carboplatin hypersensitivity reaction.\(^17\) Although carboplatin has not been associated with pathologic arrhythmias beyond sinus tachycardia, hypersensitivity reactions have been well characterized and range in severity. Mild carboplatin hypersensitivity reactions include erythema of the palms or soles, facial flushing, or pruritus.\(^6\) More severe reactions are due to generalized histamine release and can result in generalized erythema, throat and chest tightness, angioedema, or sinus tachycardia.\(^6\) Rarely, cardiac or respiratory arrest consistent with anaphylaxis can occur.\(^7\) Whether mild or severe, carboplatin hypersensitivity reactions may have a delayed onset, occurring as late as a few days after infusion.\(^18,19\) A mechanism of sensitivity is postulated to be due to a type I immunoglobulin E-mediated reaction, since the hypersensitivity reaction is not seen during the initial infusion, but rather requires a cumulative sensitization to the drug prior to development of symptoms.\(^6\) By the eighth cycle of carboplatin treatment, hypersensitivity reactions are more common, occurring in 15% of patients.\(^18\)

Given the impact that carboplatin-associated atrial arrhythmias may have on the clinical course of patients with cancer, we reported this case to the Food and Drug Administration as a potential new adverse effect. Although this patient had underlying cardiac disease and was intermittently adherent to his medications, the Naranjo probability scale score revealed a possible relationship between carboplatin and atrial flutter, especially because of the strong temporal association between the 2 events.\(^20\) The pathologic mechanism for this patient’s atrial irritability cannot be definitively known because of the lack of a postmortem examination, but other explanations were less likely. For example, he may have had atrial flutter due to direct involvement of the pericardium or myocardium with SCLC; however, diagnostic evaluation did not support tumor invasion. Noninvasive studies, including ECHO and CT imaging, showed no evidence of tumor invasion into the myocardium. Clinically, the lack of sustained changes in pulse and arrhythmic activity during home monitoring and clinic visits, independent of carboplatin infusion, also makes invasion less likely. Pericardial thickening and an effusion were noted on CT imaging 1 month prior to admission, but both had resolved when the patient developed atrial flutter. Rather than a direct effect of metastatic tumor, the initial pericardial effusion could have been explained by mediastinal disease partially obstructing the lymphatic drainage of the pericardium, resolving as SCLC responded to carboplatin and etoposide treatment.\(^21\) Alternatively, the effusion may have been a reactive pericardial effusion, as seen in 50% of patients with malignancies, resulting from chemotherapy administration or a metabolic disturbance, or it could have been of idiopathic origin.\(^22,23\)

The pericardial thickening was probably due to inflammation, since tumor involvement of the pericardium is typically right-sided and would have had an irregular and nodular appearance, which was not evident on imaging.\(^24,25\) Since manipulation of the pulmonary artery can cause atrial arrhythmias,\(^26\) the tumor compressing the right pulmonary artery could have led to the patient’s symptoms. However, pulmonary artery irritation generally causes atrial fibrillation, whereas this patient had atrial flutter. In addition, atrial flutter

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**Figure 3.** Follow-up electrocardiogram when the rhythm converted to sinus rhythm.
was transient, whereas compression of the pulmonary artery would have presumably led to a persistent tachyarrhythmia. Alternatively, the arrhythmia could have been due to a non-cardiac etiology, such as subclinical hyperthyroidism, especially with an initial TSH level of 0.24 mIU/L. Atrial arrhythmias are unlikely to occur at this TSH level, since there is no significant increase in arrhythmia risk unless the level is below 0.10 mIU/L. In this case, the TSH level was normal 1 day later, as was the thyroxine level. Other etiologies for atrial flutter could have included electrolyte derangement, systemic inflammatory response syndrome, acute myocardial injury, or concurrently administered medications. However, laboratory results do not support an electrolyte cause. Systemic inflammatory response syndrome is also an unlikely source, since data do not support an inflammatory response other than leukocytosis, which was likely a late effect from pegfilgrastim and dexamethasone therapy. The patient’s elevated troponin level was probably related to demand ischemia in the setting of a rapid ventricular rate, as he did not have any signs or symptoms to suggest acute coronary syndrome or myocarditis. Finally, it is unlikely that the medications administered prior to the carboplatin infusion triggered atrial flutter, since ranitidine, diphenhydramine, and dexamethasone are not associated with atrial tachyarrhythmias.

Rarely, ondansetron has been associated with adverse cardiac events, including hypertension, coronary vasospasm, and ECG changes. The resultant ischemia can lead to cardiac dysrhythmias, ranging from sinus bradycardia to supraventricular tachycardia to ventricular fibrillation; atrial flutter has not been described. Our patient developed atrial flutter more than 1 hour after he had received ondansetron; cardiac toxicity usually occurs within minutes of a rapid, high-dose intravenous infusion.

**CLINICAL IMPLICATIONS**

Similar to this patient, others with lung cancer have several baseline characteristics that predispose them to atrial flutter or other arrhythmias. Mainly, they are older, more likely to be male, and more likely to have preexisting cardiac disease or chronic obstructive pulmonary disease. Despite the higher risk for atrial flutter, which can be more than double the risk in the general population, there has been no study specifically looking for cardiac events or arrhythmias in patients who receive carboplatin monotherapy for lung cancer treatment. The only available data are from epidemiologic studies of children and young women with gynecologic, germ-cell, or blood cancers. In these types of patients, carboplatin did not cause arrhythmias or other major cardiac events beyond sinus tachycardia. In contrast, most lung cancer treatment regimens do not use solely carboplatin and require administration of other antineoplastic agents known to cause both bradyarrhythmias and tachyarrhythmias, making it difficult to determine the arrhythmogenic potential of carboplatin. In addition, many patients undergo radiotherapy and surgery for lung cancer, which intrinsically can cause atrial irritability.

We suggest that patients with a history of cardiac disease should be observed more closely, including more frequent pulse rate checks during carboplatin infusion and during appointments. In addition, telemetry monitoring should be considered in high-risk patients, including those with evidence of myocardial infarction on ECG, as well as history of acute coronary syndrome or other cardiac abnormalities. Clinically, the benefit of aggressively addressing cardiac arrhythmias is intuitive, since arrhythmias, including those of atrial origin, are associated with increased morbidity and mortality. Data on the prognosis of atrial arrhythmias in patients with tumors are scant; however, a reasonable hypothesis is that those with tumors and atrial flutter or other arrhythmias are prone to a poorer prognosis. Mortality rates attributed to atrial arrhythmias can be high, with one study suggesting a 7-fold increase in mortality when compared to sinus rhythm. Also, management options may be more limited in patients with cancer because the risks of anticoagulation, a mainstay in both rate control and rhythm control strategies, are significantly higher.

When considering treatment of cancer in patients with cardiovascular disease, the benefits of chemotherapy should be carefully weighed against the risks, as a number of chemotherapy agents, including platinum-based compounds, can cause adverse cardiac reactions. Specifically, cisplatin has been associated with both acute and long-term cardiac effects, including myocardial infarction and arrhythmias. Carboplatin has fewer reported cardiac effects. A literature review identified only 1 case of acute congestive heart failure and 1 patient with third-degree atrioventricular block. Furthermore, atrial flutter has not been noted. To our knowledge, this case report is the first to suggest a possible association between carboplatin infusion and atrial irritability, since other causes for atrial flutter were far less likely. The patient’s presentation was probably not idiosyncratic, since those with lung cancer may have an increased susceptibility to atrial arrhythmias. Clinically, patients with lung cancer receiving carboplatin may require more cardiac monitoring to detect tachyarrhythmias earlier. Patients with preexisting cardiac disease may be at even higher risk, suggesting the need for possible telemetry monitoring during infusion and pulse assessment during subsequent follow-up. Ultimately, this case report and literature review should spur further study, ideally a prospective cohort study, in patients with lung cancer who are receiving carboplatin, to determine the prevalence and significance of atrial arrhythmias.

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