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# Acute heart failure following platinum and taxane-based chemotherapy for high grade ovarian cancer

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## 1. Background

In the US, 10.2 out of 100,000 women are diagnosed with ovarian cancer every year (Cancer of the Ovary—Cancer Stat Facts, n.d). Ovarian cancer is known to be aggressive and is often diagnosed at advanced stages. A crucial component of treatment for ovarian cancer is chemotherapy. Per National Comprehensive Cancer Network (NCCN) guidelines, the first-line chemotherapy agents for ovarian cancer are carboplatin and paclitaxel (National Comprehensive Cancer Network, n.d.). Although neoadjuvant chemotherapy has been cited with reduced postoperative complications and surgical complexity compared to adjuvant therapy, it is still accompanied by the risks of side effects and adverse events (Chiofalo et al., 2019). Discussion about the possibility of adverse reactions is an important component of pretreatment counseling with patients prior to chemotherapy initiation. This includes review of the most common side effects attributed to the selected agents.

The commonly reported side effects of carboplatin are metabolic, gastrointestinal, and hematologic disturbances. Cardiac adverse events associated with carboplatin are rarely reported. Commonly adverse effects of taxanes include gastrointestinal, dermatologic, and hematologic reactions. Cardiac events are less prevalent in the literature. They have been cited to occur in 3–20% of patients receiving taxanes (Batra et al., 2021; Rowinsky et al., 1991). These cardiac events are more often related to arrhythmias. The proposed mechanism of action is thought to be secondary to histamine mediated hypersensitivity reaction, which disrupts the cardiac conduction system. Heart failure with use of taxanes is less commonly reported; its incidence is reported to range from 2.3% to 8%, and to our knowledge has yet to be reported following the first cycle of chemotherapy (Curigliano et al., 2010). This case report describes a patient with high grade ovarian cancer who experienced acute cardiomyopathy with left ventricular dysfunction following the first cycle of neoadjuvant carboplatin and paclitaxel.

## 2. Case report

We report a case of a 73-year-old Black woman who presented for gynecologic oncology consultation after diagnosis of metastatic high-grade mullerian carcinoma following liver biopsy. Her past medical history at initial presentation was significant for diabetes, hypertension, and a history of pulmonary embolism on two occasions on lifelong anticoagulation. Significant medications at the time of consultation were apixiban 2.5 mg twice daily, glipzide 5 mg daily, metformin 1000 mg twice daily, and losartan 25 mg daily. Five months prior to her gynecologic oncology initial consultation visit, the patient underwent a transthoracic echocardiogram due to new onset shortness of breath and palpitations in the setting of her history of provoked pulmonary embolism. The echocardiogram at that time demonstrated an estimated ejection fraction of 55 to 60%, normal right ventricular size and systolic function, and mild annular calcification. Her pro B type natriuretic peptide at that time was normal at 74. At that time of her gynecologic oncology consultation visit 5 months later, the symptoms of shortness of breath and palpitations had resolved. Given her hepatic involvement, her initial treatment plan was 3 cycles of neoadjuvant chemotherapy that consisted of carboplatin area-under-curve (AUC) 5 and paclitaxel 175mg/m2 every 21 days prior to consideration of cytoreductive therapy.

She completed cycle 1 of carboplatin AUC 5 and paclitaxel 175mg/m2 (Fig. 1). On day 18 of cycle one, the patient developed acute dyspnea on exertion. Initial evaluation in the emergency department was notable for the following: an EKG with sinus tachycardia and new T-wave inversions on leads I and aVL, troponin levels of 48 and repeat of 47 (normal range at our institution < 37), pro B type natriuretic peptide of 193 (normal range at our institution is < 100), and CTA with mild pulmonary venous congestion and bilateral effusions but negative for pulmonary embolism. Per cardiology recommendation, a transthoracic

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echocardiogram was performed which showed an estimated ejection fraction of 15 to 20% and "severely decreased global left ventricular systolic function." She was diagnosed with acute cardiomyopathy with notable left ventricular dysfunction. An extensive cardiac evaluation during her hospitalization was performed, which included a cardiac MRI, cardiac PET, and cardiac CT stress testing. This evaluation for both anatomic and functional ischemia showed no clear etiology of the acute reduced ejection fraction heart failure. Cardiac MRI demonstrated evidence of left ventricular dilation with an end-diastolic volume index of 108 mL/m2. In addition, there was no evidence of T2 enhancement to suggest acute inflammation or edema. There was no evidence of late gadolinium enhancement. Small pericardial effusion was noted without constriction. Platinum-based regimens have been associated with acute coronary syndromes hypertension and endothelial dysfunction. However, cardiac stress testing demonstrated normal coronary flow reserves without evidence of myocardial ischemia or infarction. She was started on a 4-drug regimen of metoprolol succinate, sacubitril/valsartan, spironolactone, and empagliflozin.

Without clear etiology, her recent chemotherapy was suspected to be the inciting factor of the patient's acute heart failure. Her next chemotherapy treatment was delayed. She underwent an echocardiogram one week after her hospitalization which demonstrated an unchanged estimated ejection fraction of 15 to 20%. After speaking with oncology pharmacists, gynecologic oncologists, and medical oncologists at several cancer centers, a consensus was not reached about the cause of the patient's heart failure. Thus, two options were presented. The first was to administer carboplatin and paclitaxel in a hospital setting or transition to cisplatin, allowing the patient to receive platinum therapy as it is the more active agent in the chemotherapy combination. A joint decision was made to proceed with cisplatin. She received cisplatin 60 mg/m2. The intravenous fluid was adjusted to 250 mL and was administered over 2 h, and 40 mg of IV furosemide was given post-treatment. Additionally, she was instructed to take 40 mg of furosemide and spironolactone 50 mg daily on cycle day 2 and 3. Her GFR decreased from 71 to 44 following 1 cycle of cisplatin 60 mg/m2. Due to concern for nephrotoxicity, cycle 3 was changed to single-agent carboplatin. The patient tolerated this change without an adverse event. An interval CT abdomen and pelvis following cycle 3 of neoadjuvant chemotherapy showed disease improvement although persistent intraparenchymal and posterior liver disease was noted. The risks and benefits of adding paclitaxel to her cycle 4 treatment were discussed and the patient agreed. She then underwent cycles 4 to 6 with carboplatin and paclitaxel without evidence of worsening cardiac status. Following cycle 6, a CT abdomen and pelvis was performed and showed no evidence of disease in the chest, small mesenteric and peritoneal nodules, and stable hepatic lesions. She was evaluated by cardiology 2 weeks before surgery for surgical safety assessment. The patient was counseled by her cardiologist about her moderate risk of surgical complication relating to heart failure. This counseling was given in the setting of a 40% one-year mortality rate based on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data (Samman-Tahhan et al., 2018). Additionally, she was counseled that invasive cardiac monitoring would be required and the extent of intervention (i.e. arterial line and/or central line) would be at the discretion of anesthesia. The anesthesiologist for the case is boarded in cardiac anesthesia and was involved with her care weeks prior to her surgery. She successfully underwent radial resection of pelvic tumor for optimal cytoreduction with exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, posterior peritonectomy, omentectomy, Argon beam ablation, excision of retroperitoneal and diaphragmatic tumors, and cystoscopy with left ureteral stent placement and removal. A transthoracic echocardiogram in the post-operative period, 5 months from the diagnosis of acute heart failure, showed improvement of left ventricular function noted by an ejection fraction of 45–50%.

## 3. Discussion

Acute cardiomyopathy in the setting of recent carboplatin and paclitaxel infusion has been reported in the literature in a few instances. However, the distinguishing factor from our patient is the timeline of the cardiac event. Nati-Castillo et al describe an incident of stress cardiomyopathy following carboplatin and paclitaxel infusion in the treatment of stage IV cervical cancer. This event occurred following the third cycle of the combination chemotherapy while our patient developed heart failure after 1 cycle (Nati-Castillo et al., 2024).

A hypersensitivity reaction was considered. However, delayed hypersensitivity reactions typically occur 7–10 days after treatment, and when impacting the heart, they typically present as myocarditis (Pilcher, 2024). This was not consistent with our patient's clinical picture.

With the guidance of our cardiology colleagues, our patient underwent an extensive cardiac work-up, which did not reveal a clear explanation of etiology. These findings in comparison with her normal cardiac evaluation months prior to chemotherapy, supported the theory of a chemotherapy reaction as the inciting factor of her acute heart failure. We chose to alter the subsequent cycle to a different agent due to the lack of guidance from current literature. A single agent regimen of cisplatin was used for cycle 2. However, due to the development of severe nephrotoxicity following cycle 2 and the patient's symptomatic improvement from a cardiac standpoint, we discussed and ultimately decided on a retrial of carboplatin for cycle 3. After completion of cycle 3 without adverse events, paclitaxel was added to cycles 4 to 6 and no adverse events were experienced.

The precipitating factor for acute heart failure in our patient remains unclear. While there are data highlighting increased incidence of cardiac dysfunction in patients receiving paclitaxel, this is primarily cited when it is combined with anthracyclines (Page et al., 2016). In contrast,

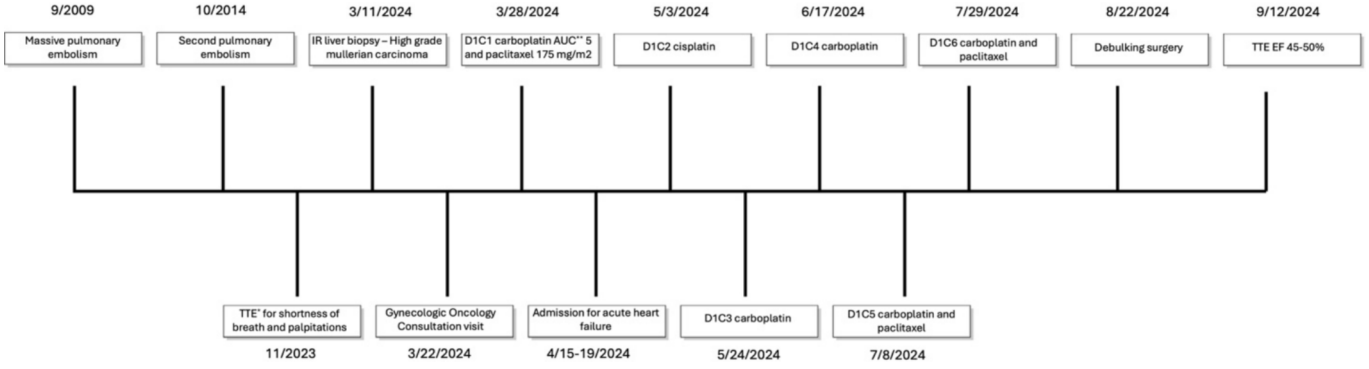


**Fig. 1.** Timeline of medical events before and after the development of acute heart failure. Clinically relevant medical events leading to the development of acute heart failure following platinum and taxane-based chemotherapy for high grade ovarian cancer is illustrated in this figure. Figure abbreviations: *TTE – transthoracic echocardiogram; **AUC – area under the curve.

carboplatin is not noted to be a cardiotoxic agent in the current literature. Hypertension is the only cardiac adverse event noted with carboplatin in post-marketing (Carboplatin: Drug Information, 2024). Although the incidence for cardiac events is low in those undergoing therapy with carboplatin and paclitaxel, completing a thorough cardiac evaluation may be considered prior to initiating therapy. When severe cardiac events arise, interdisciplinary coordination and discussion between the gynecologic oncologist and cardiologist is crucial to providing the patient with comprehensive care.

**Consent**

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions:

Danielle Lewis, MD – investigation, writing – original draft preparation, visualization

Jerry John, MD – investigation, writing – review & editing.

Shannon Armbruster – conceptualization, investigation, supervision, writing – review & editing.

## CRediT authorship contribution statement

**Danielle Lewis:** Writing – original draft, Visualization, Investigation. **Jerry John:** Writing – original draft, Investigation. **Shannon D. Armbruster:** Writing – review & editing, Supervision, Investigation, Conceptualization.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported under the National Center for Advancing Translational Science of the National Institutes of Health Award UL1TR003015/KL2TR003016, as Dr. Armbruster is a KL2 Scholar.

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