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Case Report

Possible Lurbinectedin-associated Cardiotoxicity in a Patient with Metastatic Small Cell Lung Cancer: A Case Report

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Abstract

Background: It has been a major challenge finding an effective second-line therapy with a favorable safety profile for metastatic small cell lung cancer (SCLC) in patients who failed or relapsed following first-line platinum-based chemotherapy. Lurbinectedin was approved for SCLC in patients who relapsed or failed first-line treatment. The most common adverse event associated with it was myelosuppression. Till date, no cardiotoxicity has been described with this medication in the literature.

Case Presentation

We report an unusual case of acute cardiotoxicity following commencement of lurbinectedin in a 51-year old female with a history of metastatic SCLC, who despite receiving platinum-based dual chemotherapy durvalumab, continued to show progression of the disease. She presented to the ER 2 days after receiving lurbinectedin, with sudden onset of shortness of breath, hypotension and tachycardia. Electrocardiogram showed sinus tachycardia, troponin was elevated and echocardiogram revealed severely reduced systolic function and diffuse hypokinesis with no identifiable regional variations. Lurbinectedin was discontinued. She was intubated due to worsening respiratory distress, started on vasopressors and pulse dose methylprednisolone. Repeat echocardiogram showed improved systolic function (55% - 60%). Her clinical condition also improved and she was successfully intubated. After extensive discussion about goals of care, the decision was to make the patient comfortable and DNR/DNI. She however unfortunately expired a few days after.

Conclusion: Clinicians and Oncologists should be aware of the potential of lurbinectedin to cause cardiotoxicity and further observational studies are needed to examine this association.

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Keywords: Small cell lung cancer; Lurbinectedin; Second-line treatment; Cardio-toxicity.

Background

Lung cancer of the small cell type (SCLC) represents 13% of all lung cancer diagnoses and carries a poor prognosis due to its high-grade neuroendocrine nature [1,2]. More than 60% of patients who receive platinum-based chemotherapy as a first-line treatment show an initial response that can be dramatic with rapid resolution of the disease. The disease, however, often progresses within months, and overall survival is generally less than a year [3,4]. In cancers with a high mitotic rate and a high mutation burden, such as SCLC, the clinical course is usually aggressive [5]. SCLC is particularly susceptible to compounds that inhibit transcription such as MYC genes, resulting in decreased expression of super-enhancer-associated transcription factors [6].

Lurbinectedin works by inhibiting oncolytic transcription and is used to treat small-cell lung cancer (SCLC) [7]. In the minor groove of DNA, the drug covalently binds to the Guanine of various nucleotide triplets to form adducts leading to double-strand breaks (Figure 1). The damage to DNA ultimately results in the apoptosis of the cells [8]. Furthermore, the drug is also capable of causing immunogenic cell death (ICD) as well as stimulating the immune system to neutralize cancerous cells [9]. A significant reduction in tumor-associated macrophages has also been associated with Lurbinectedin. Therefore, it is possible that the drug may also affect the microenvironment of the tumor directly [10]. The current recommendation for lurbinectedin is 3.2 mg/m2 administered intravenously once every 21 days until disease progression. Lurbinectedin has been approved by regulatory agencies in the United States for the treatment of SCLC as well as for the treatment of metastatic SCLC with disease progression in patients following platinum-based chemotherapy [11-13].

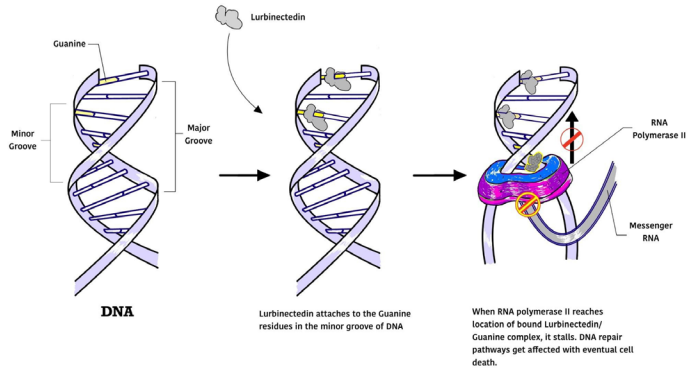

Figure 1: Mechanism of Action of Lurbinectedin.

In clinical trials, lurbinectedin monotherapy for SCLC has been associated with myelosuppression as the most frequent clinically significant adverse reaction [14]. A study of 105 patients found that myelosuppression was associated with anemia in 91.4% of the patients, neutropenia in 68.6%, and thrombocytopenia in 41.9% of the patients. Other adverse events include nausea/vomiting, diarrhea, fatigue, and elevated liver enzymes. In particular, patients with increased ALT, AST, and ALP levels were found in 68.6%, 42.9%, and 31.4% of cases, respectively. [16]. To date, there have been no reports in the literature of cardiotoxicity associated with lurbinectedin use in SCLC. Herein, we describe the case of a patient who presented to the hospital with acute heart failure after the initiation of lurbinectedin.

Case presentation

Our patient was a 51-year old female with metastatic SCLC (liver, adrenal and bones with osteoblastic lesions). She was brought in by EMS on account of shortness of breath which was said to have developed after waking up from sleep in the morning. There was no history of chest pain, cough, nor leg swelling. There was no history of recent travel or oral contraceptive use. Patient has a history of tobacco smoking and COPD; she admitted that her current episode of breathlessness was different and worse than previous episodes of COPD exacerbation.

Prior to presentation, the patient had received five cycles of durvalumab (initially combined with carboplatin/etoposide and then 2 further doses as maintenance for the SCLC); ECHO showed normal cardiac function while on durvalumab which she received for about 6 weeks.The disease however continued to progressed as evidenced by diffuse osteoblastic bone lesions on CT scan even while on the maintenance therapy and was switched to a combination therapy of lurbinectedin and doxorubicin. She developed shortness of breath two days after commencing lurbinectedin, prior to starting doxorubicin. Cardiovascular work up with echocardiogram, EKG and N-Terminal pro-brain natriuretic peptide before commencement of the medication, were unremarkable.

Significant findings on examination were hypotension, tachycardia, hypoxia and increased work of breathing. Patient was intubated for airway protection. Initial laboratory workup on admission was significant for elevated troponin of 0.215 (reference <0.034) and N-Terminal pro-brain natriuretic peptide of 10,700 pg/mL (reference 11.1 - 125.0). There was mild hyponatremia of 125 mEq/L (reference 133-145) Prechemotherapy EKG showed old Anteroseptal infarct (Figure 2), admitting EKG revealed sinus tachycardia, slightly coved ST elevation in V1 and 2 with T wave inversions (Figure 3).

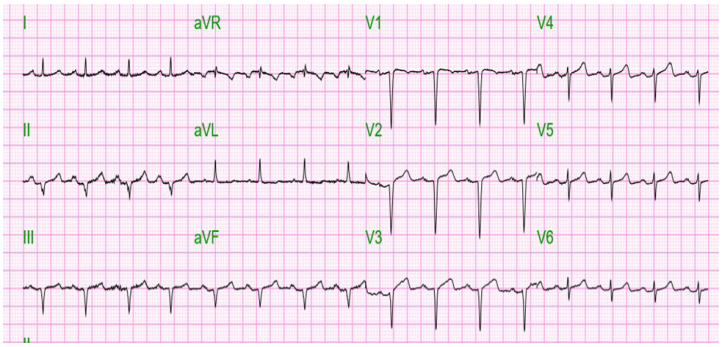

Figure 2: Pre chemotherapy EKG.

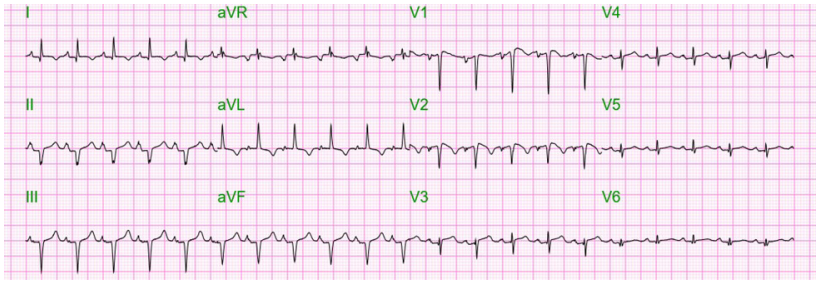

Figure 3: Admitting EKG showing Brugada pattern.

Chest X-ray was revealed interstitial opacities suggestive of pulmonary edema, and bilateral pulmonary nodules. Computerized Tomography angiogram of the chest was negative for pulmonary embolism. Echocardiogram was technically difficult and suboptimal images were acquired, findings revealed severely reduced systolic function with an ejection fraction estimated in the range of 20% to 25% and significant diffuse hypokinesis with no identifiable regional variations (Figure 4a-4b).

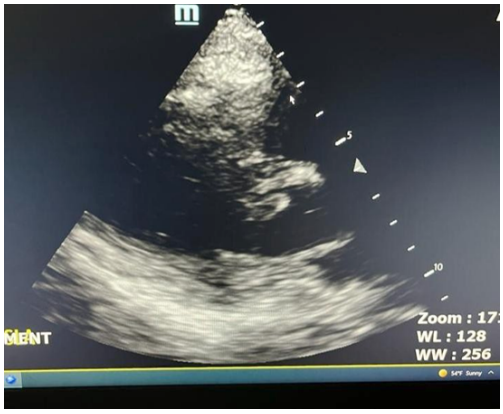

Figure 4a: 2D ECHO showing dilated Left ventricular chamber.

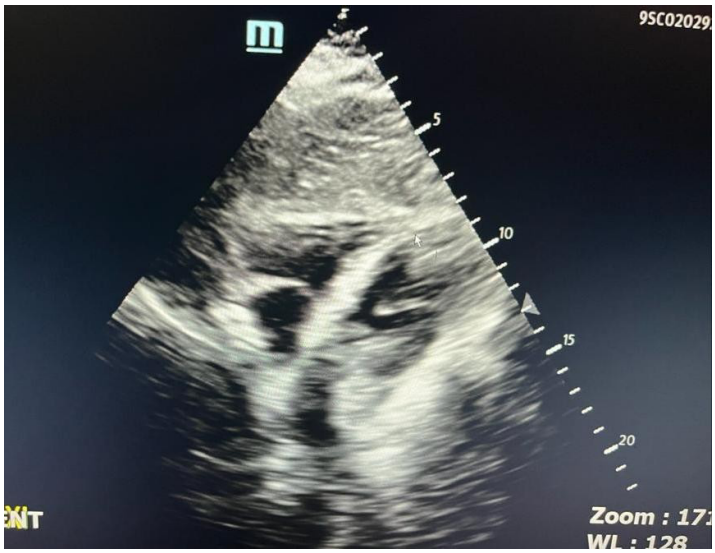

Figure 4b: 4 chamber-2D ECHO showing subcostal view.

Patient was intubated for airway protection and started on vasopressors (norepinephrine and milrinone infusion) for suspicion of cardiogenic shock. She was also commenced empirically on pulse dose methylprednisolone due to concerns of chemotherapy-induced myocarditis. Due to unstable condition and advanced stage of the lung cancer of the patient, she was deemed not a candidate for cardiac MRI, endomyocardial biopsy or cardiac catheterisation as her life expectancy was already less than a year from her cancer diagnosis.

Repeat ECHO following steroid course showed improved systolic function (EF of 55% to 65%) and EKG revealed new widespread T waves changes (Figure 5); however, concomitant troponin was unremarkable. Suspicion of obstructive coronary artery disease was remote and Coronary angiography was contra-indicated in the setting of advanced metastatic SCLC with short life expectancy. Patient's mental status improved and could respond to commands. She was extubated after a successful spontaneous breathing trial. She however deteriorated post-extubation, as she became less responsive to any stimuli. Goals of care were discussed with family who wanted her to be DNR/DNI with no pressors. Patient unfortunately expired a few days after presentation.

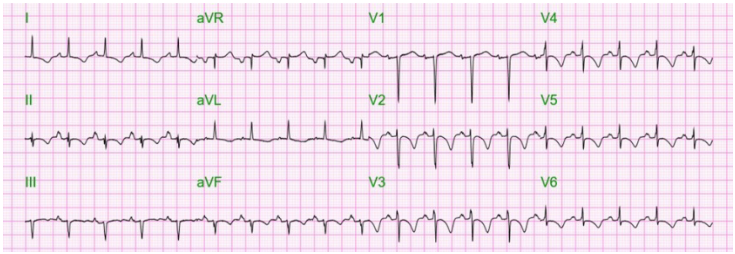

Figure 5: Repeat EKG showing diffuse T wave inversion.

Discussion

Small cell lung cancer is one of the most aggressive forms of lung cancer with an overall 5-year survival that is less than 10% and 9-11 months in the metastatic form [15-17]. Cardiotoxicity is a common adverse event associated with chemotherapy which can worsen outcomes [18,19]. There is no universal definition of chemotherapy-associated cardiotoxicity. The committee that supervised trastuzumab clinical trials defined it as one or more of the following: 1) cardiomyopathy evidenced by a reduction in left ventricular ejection fraction (LVEF); 2) symptoms and signs associated with heart failure; 3) reduction in LVEF from baseline that is in the range of less than or equal to 5% to less than 55% with accompanying signs or symptoms of HF, or a reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without accompanying signs or symptoms [20].

Cardiotoxic effects of chemotherapy could be acute in which they occur from the initiation of cancer treatment up to 2 weeks after completion of therapy; it is early chronic if they appear more than 2 weeks but less than 1 year of completion of treatment, and late chronic if more than 1 year of treatment [21]. Mechanisms of chemotherapy-induced cardiotoxicity include direct cellular injury resulting in structural changes that can impair ejection fraction, arrhythmias and inflammation involving the myocardium with/or pericardium [21, 22].

Prior to 2020, topotecan (a topoisomerase 1 inhibitor) was the only approved second-line treatment for SCLC patients. However, in June 2020, lurbinectedin was approved by the U.S. Food and Drug Administration (FDA) as a second-line therapy for relapsed or refractory SCLC based on the positive responses reported by a basket trial involving patients with SCLC [23,24]. In a pooled safety analysis comparing lurbinectedin and topotecan, the former fared significantly better than the later as there were less severe hematological toxicities, adverse events, need to adjust dose, incidence of discontinuation of treatment, and there was more use of supportive treatments in lurbinectedin-treated patients [25].

Lurbinectedin is a selective inhibitor of transcription and it does this by binding to CG-rich sequences predominantly in the promoters of protein-coding genes, inhibits and degrades elongating RNA polymerase II on the DNA template and generates DNA breaks and ultimate apoptosis [1]. In addition to tumor suppression, it may play a role in matrix remodeling and inhibiting angiogenesis in the microenvironment of the tumor. The most common adverse event described with lurbinectedin was myelosuppression predominantly leukopenia [23,25]. Cardiotoxicity has never been described with it in contrast to an identical drug trabectedin, which is used in the management of patients with advanced soft tissue sarcoma and generally thought to be non-cardiotoxic; there was a report of cardiotoxicity associated with trabectedin use reported in the literature [26].

Our patient received durvalumab which she initially was on, but later discontinued due to poor response and switched to lurbinectedin. Cardiotoxicity has been reported with durvalumab [27,28] but there is presently no documented evidence of its association with lurbinectedin. Following the approval of lurbinectedin, a group of researchers investigated the effect of the medication on the QTc interval in patients with advanced solid tumors and found out that the therapy was not associated with clinically significant effect on cardiac repolarization [29].

Our patient received five cycles of durvalumab (initially combined with carboplatin/etoposide and then two further doses as maintenance for the SCLC) with no evidence of cardiotoxicity during the treatment course. However, due to progression of the disease while on the maintenance therapy, she was consequently switched to a combination chemotherapy with doxorubicin and lurbinectedin maintenance.

She however developed adverse cardiac effects two days after starting lurbinectedin, before commencement of doxorubicin. Maetani et al. [28], reported a case of delayed cardiotoxicity in a patient with non-small cell lung cancer occurring about 7 months after first administration with durvalumab (patient had a total of 14 course of durvalumab every 2 weeks over a 7-month period). Our patient received 5 cycles of durvalumab every 3 weeks over a 3.5 month period; the last dose was given about 6 weeks prior to commencement of lurbinectedin. We find it difficult to ascertain if the cardiotoxic effects identified in this patient were due to delayed sequelae of durvalumab, purely from lurbinectedin or a combination of both. However, the timing and acute onset of cardiac dysfunction following initiation of lurbinectedin is highly suggestive that the lurbinectedin was most likely the inciting agent rather than a delayed sequela of durvalumab.

If cardiotoxicity in this patient was due to delayed sequelae of durvalumab, our case will be the first report of this adverse event associated with this medication in the setting of small lung cancer in the literature. However, if cardiotoxicity was due to lurbinectedin, this also will be the first reported case of cardiac dysfunction associated with the drug.

More observational studies are needed to examine this association. We believe it is pertinent to raise an awareness of the possibility of occurrence of cardiotoxicity with lurbinectedin and/or durvalumab in patients with small cell lung cancer. We strongly recommend more pharmacovigilance as regards the use of these agents. Clinicians should be aware of this potential adverse event occurring with these medications when making decisions regarding a second-line therapy in the management of patients with SCLC.

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