Accidental, Iatrogenic Overdose of Experimental Chemotherapy Drug AL3818/Anlotinib: A Case Report

Vinay Saggar[1*] and Andrew Restivo

[1]Department of Emergency Medicine, New York-Presbyterian/Weill Cornell Medicine and Columbia Vagelos College of Physicians and Surgeons, New York, United States of America
[2]Department of Emergency Medicine, Albert Einstein College of Medicine/Jack D. Weiler Hospital, Bronx, New York, United States of America

Corresponding Author*

Vinay Saggar
Department of Emergency Medicine, NewYork-Presbyterian/Weill Cornell Medicine and Columbia Vagelos College of Physicians and Surgeons, New York, United States of America
E-mail:

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Abstract

AL 3818 (Anlotinib, Catequentinib), a novel multi-target tyrosine kinase inhibitor that is administered orally, is recently undergoing phase Ib/IIa trials in patients with recurrent or metastatic endometrial, ovarian or cervical carcinoma3. This is a case of a patient with stage IIIA2 serous ovarian adenocarcinoma who accidentally ingested twelve times the desired amount of Advenchen AL3818/anlotinib. The patient's initial ED resuscitation strategy revolved around intravenous fluids, prompt administration of activated charcoal, and coordination of an endoscopic retrieve attempt which was ultimately unsuccessful. The patient subsequently developed downstream sequela of acute renal injury and stress-related taksubo cardiomyopathy. Although just one case–and to our knowledge the first of its kind–of Advenchen AL3818/anlotinib overdose, this report suggests these patients should have a wide array of "screening" labs sent and strong consideration for prolonged observation periods given the potential of delay complications that can arise.

Keywords: Cytokine release syndrome • Immune checkpoint inhibitors • ICANS

Introduction

Ovarian cancer is the fifth leading cause of cancer-related death among women, accounting for more deaths than any other cancer of the female reproductive system [1]. This cancer commonly develops in women aged 40 and older, and currently, treatment revolves around surgical debulking and chemotherapy [2]. AL 3818 (Anlotinib, Catequentinib), a novel multi-target tyrosine kinase inhibitor that is administered orally, has recently undergone phase Ib/IIa trials in patients with recurrent or metastatic endometrial, ovarian or cervical carcinoma [3]. Its efficacy and safety profile are currently under assessment in this patient population.

We present a case of a patient with stage IIIA2 serous ovarian adenocarcinoma who accidentally ingested twelve times the desired amount of Advenchen AL3818/anlotinib. This case demonstrates possible downstream sequela of acute renal injury and stress-related taksubo cardiomyopathy in its overdose.

Case Report

The patient was a 69-year-old G0 female with stage IIIA2 serous ovarian adenocarcinoma with recurrence and progressive disease despite multiple chemo regimens and debulking. She was enrolled in Advenchen AL3818/anlotinib trial for the treatment of her cancer and initially presented to the Emergency Department after an accidental, iatrogenic chemotherapy overdose. The patient was given a bottle of ANLOtinib in her GYN/ONC clinic 20 minutes before arrival. She took twelve 8mg pills instead of one 8 mg pill. When the patient first arrived, she complained of mild nausea but no chest pain, shortness of breath, abdominal pain, vomiting, or other acute symptoms. She was hemodynamically stable, generally well appearing with a non-tender abdomen and an unremarkable cardiopulmonary exam. The patient was administered a 2L IV bolus of LR and 100 g of activated charcoal PO (weight-based) and poison control was contacted. They agreed with our initial resuscitative efforts and stated that given the lack of accessible data, there was no antidote available but suggested gastric lavage (which was not attempted in the ED).

The initial labs for the patient showed notable rising creatinine of 1.22 from 1.04 the morning before arrival, slightly elevated poBNP 790 and troponinemia of 2.66 (no baseline to compare from the morning), but a normal EKG, sinus rhythm, normal QTc, and without ST elevation/depression.

Within 3 hours of the patient's hospital course and in coordination with GYN/ONC, Anesthesia, and GI, she underwent an emergent EGD which was unsuccessful at retrieval or visualization of the tablets. At that point, the decision was made for the patient to remain intubated overnight due to fullness of the stomach and risk of aspiration. Renal was consulted for possible benefit of dialysis but given anlotinib was noted to have a large volume of distribution and highly protein bound, it was presumed unlikely to be removed by hemodialysis.

The patient was successfully extubated on day 2 of hospitalization without complications and serial labs showed a peak Cr of 1.37, troponin of 3.78, and proBNP of 1353 that all downtrended and nearly resolved by day 3 (aside from the proBNP). EKGs remained unchanged and the rest of the blood work remained near baseline. The patient had an ECHO done which showed dilated LV with decreased EF 25% that was thought to be stress-related taksubo cardiomyopathy. Cardiology was consulted where the patient was started on aspirin (day 2) and then GDMT of beta blocker and statin (day 3) once labs had stabilised and no signs of bleeding had shown.

The patient remained hemodynamically stable throughout her hospital course and eventually was discharged within a week of hospitalization to SAR per OT/PT recommendations given fatigue and weakness after the prolonged hospital course.

Discussion

Anlotinib is a novel multi-target Tyrosine Kinase Inhibitor (TKI) that inhibits angiogenesis via suppressing the activation of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), platelet-derived growth factor receptor β (PDGFRβ) and Fibroblast Growth Factor Receptor 1 (FGFR1) [4]. To date,

clinical studies have shown that anlotinib can effectively prolong the Overall Survival (OS) and Progression-Free Survival (PFS) of advanced non-small cell lung cancer [5], small cell lung cancer [6], oesophagal squamous cell carcinoma [7], metastatic colorectal cancer [8], and soft tissue sarcoma [9]. Currently, it is being studied as a possible treatment for ovarian, endometrial, and cervical cancers.

Prior studies have shown that the most common adverse events from anlotinib include hyperlipidemia, hypothyroidism, hand-foot skin reaction, hypertension, abnormal myocardial enzymes, prolonged QT, risk of coagulopathy with spontaneous bleeding, and neutropenia among others [10,11]. Currently, under phase Ib/IIa trials for efficacy and safety in recurrent or metastatic endometrial, ovarian or cervical carcinoma, patients enrolled in Advenchen AL3818/anlotinib have also commonly endorsed arthralgias, asthenias, back pain, and diarrhoea when tolerating the medication [3].

To our knowledge, there are no case reports that describe the downstream sequela of Advenchen AL3818/anlotinib overdose. The purpose of this case report is to assist physicians in this rare but possible event. This case exemplifies the need for serial blood work and monitoring, given our patient developed worsening AKI and tropinemia on day 2 of hospitalization. Our patient also developed stress-related takotsubo cardiomyopathy as seeded by the ECHO during hospitalization, further corroborating the need for prolonged monitoring to ensure delayed decompensation does not occur.

Our case is also unique in being the first to have EGD attempt to retrieve the ingested pills. Although the intervention occurred three hours after ingestion and attempts for retrieval were done well after the administration of charcoal, it is significant to note that visualization of the pills was found to be unsuccessful. This may be particularly problematic given anlotinib's large volume of distribution and profile for being highly protein-bound in animal studies [11,12] presumingly making it highly unlikely to be removed by hemodialysis.

It is important to note that this is just one presentation of Advenchen AL3818/anlotinib overdose. Many factors including patient profile, time from and amount of ingestion, interventions done, and others play a pivotal role in the downstream sequela of similar presentations. Therefore, as always it will be necessary to continue to collect and report cases of Advenchen AL3818/anlotinib overdose.

Conclusion

Our case is the first of its kind to describe the downstream sequela and attempted emergent intervention of Advenchen AL3818/anlotinib overdose. We advocate that a wide array of "screening" labs be sent to these patients and that providers strongly consider prolonged observation periods in these patients given the potential of delay complications that can arise.

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