



## SCIENTIFIC LETTERS

### Treatment with carfilzomib. Should these patients be admitted to the Intensive Care Unit?<sup>☆</sup>



### Tratamiento con carfilzomib. ¿Deberían estos pacientes ingresar en la unidad de cuidados intensivos?

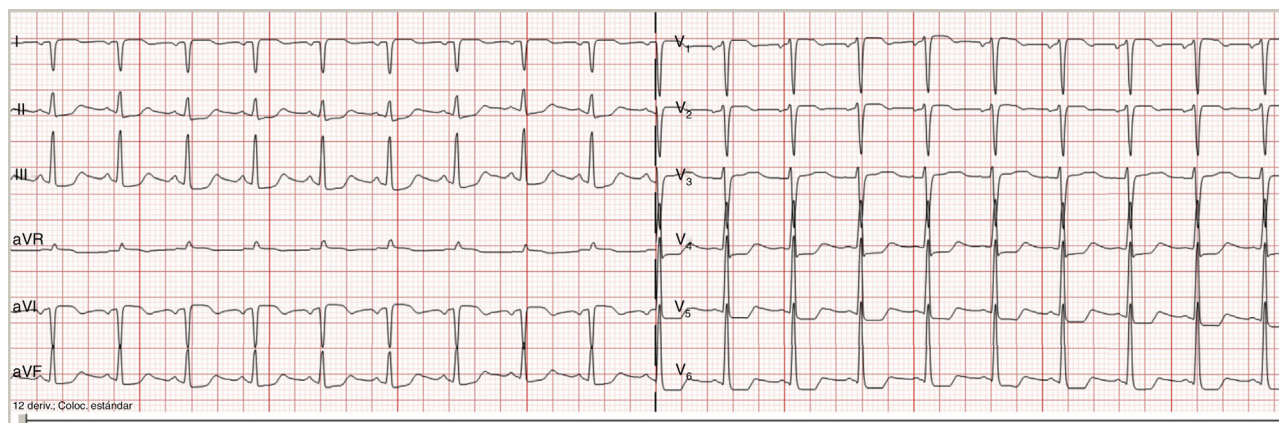
The new drug treatments for different hematological neoplasms have improved the prognosis of these diseases by expanding the available therapeutic options. However, these drugs are not free from side effects that can be potentially life-threatening for the patient. Considering the potential hazards, it is necessary to determine whether the use of such drugs requires protocolized admission to the Intensive Care Unit (ICU) of patients considered to be at risk, in order to guarantee strict vigilance and monitoring.

We present the case of a 56-year-old male with multiple myeloma, no other clinical antecedents of interest, and no previous heart disease who suffered cardiac arrest following the administration of chemotherapy with carfilzomib (Kyprolis<sup>®</sup>). The patient was diagnosed with multiple myeloma (IgG, initial stage IIIA, ISS-I) in 2003 and received radiotherapy, chemotherapy, rescue therapy with hematopoietic stem cells, and posterior consolidation in the form of autogenous transplantation. Two transthoracic echocardiographic studies (in 2011 and 2012) revealed mild tricuspid and mitral valve insufficiency, with no other relevant alterations. Following complete remission, biological progression was observed in 2012. Despite administration of a new chemotherapy cycle, a progressive increase in the monoclonal component was noted, with multiple hypermetabolic foci corresponding to tumor infiltration. Therapy was started with pomalidomide, dexamethasone and cyclophosphamide. Since this treatment proved ineffective and disease progression was observed, alternative treatment was considered in the form of carfilzomib, lenalidomide and dexamethasone (KRd). Treatment with carfilzomib was started with no prior echocardiographic study. The dosing scheme was 20 mg/m<sup>2</sup> on days 1 and 2 of the cycle, and 27 mg/m<sup>2</sup> on days 8, 9, 15 and 16. The first cycle proved uneventful, though during infusion of the second cycle,

28 days later, the patient suffered sudden dyspnea and febrile syndrome with the second dose, requiring admission to the Department of Hematology. Under conditions of hypotension, poor perfusion and acute respiratory failure, a brain CT scan and thoracic angioCT study were made, which discarded pulmonary embolism and brain disease. Echocardiography in turn revealed mild-moderate mitral valve insufficiency and mild tricuspid valve insufficiency, with the estimation of a systolic pulmonary artery pressure of 37 mmHg. Empirical antibiotic treatment was started, with fluid therapy and oxygen therapy, followed by clinical improvement. However, 3 h later the patient presented acute lung edema followed by cardiac arrest. The usual cardiopulmonary resuscitation maneuvers were applied during 5 min, with the administration of 1 mg of adrenalin, after which rhythm recovery in atrial fibrillation was observed, and the patient was moved to the ICU. The chest X-rays confirmed the diagnosis of acute lung edema, exhibiting a “butterfly wing” pattern, with perihilar redistribution and cardiomegalia. The ECG tracing showed ST-segment depression on the inferolateral aspect (Fig. 1), with no significant enzyme changes (troponin T 53 ng/l). Coronary angiography was not performed, since the patient referred no chest pain suggestive of ischemic heart disease, and the electrocardiographic changes were set in the context of cardiac arrest. Treatment was provided in the form of furosemide, corticosteroids and antibiotics, followed by good neurological, hemodynamic and respiratory recovery. Monitoring revealed no new electrocardiographic changes, and discharge was therefore decided 48 h after admission. The cardiac event was considered to probably constitute a side effect of carfilzomib. Over the subsequent days the patient again suffered clinical worsening due to progression of his hematological disease. The patient rejected the continuation of medical treatment and died in the Hematology ward 10 days later.

Carfilzomib, authorized in 2012, is a potent second-generation 20S proteasome chymotrypsin type activity inhibitor used to treat refractory multiple myeloma and other diseases such as Waldenström's macroglobulinemia, lymphoma amyloidosis and certain autoimmune diseases.<sup>1</sup> The drug is administered via the intravenous route in an interval of about 10 min. Dexamethasone premedication is advised in order to minimize the intensity of frequent symptoms such as fever, nausea, fatigue or headache.<sup>2</sup> Carfilzomib has a broad range of adverse effects, from transfusion reactions to both hematological (thrombocytopenia and anemia) and non-hematological complications.<sup>3</sup> The PX-171-007 trial reported that a high dose of carfilzomib results in greater efficacy than the approved dose<sup>4</sup> of 27 mg/m<sup>2</sup>, though higher doses also increase the risk of

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**Figure 1** Electrocardiogram: sinus rhythm with ST-segment depression on inferolateral aspect.

cardiovascular adverse events. Carfilzomib is characterized by low peripheral neuropathy rates (such complications being common with other therapeutic regimens based on bortezomib), though recent case series and studies indicate that treatment with proteasome inhibitors can be associated to serious cardiac events.<sup>5</sup> The initial clinical trials recorded episodes of heart problems with congestive heart failure, lung edema and a decrease in left ventricular function in 7% of the patients—the most frequently described adverse events being arrhythmias, most of which were of a benign nature and of supraventricular origin.<sup>6</sup> More recent publications report a large number of cardiac complications. Danhof et al.<sup>7</sup> described serious adverse effects in 50% of the patients, with left heart failure in 23%. The risk of cardiac adverse events was higher in patients concomitantly receiving doxorubicin or thoracic radiotherapy, as in our case. Careful patient selection is therefore advised, with close monitoring of the population at risk. [Table 1](#) describes the adverse effects and risk factors for cardiac toxicity.

It has been postulated that the cardiovascular effects can be mediated by different mechanisms derived from proteasome inhibition. The most important of these mechanisms is the accumulation of damaged and non-degraded proteins within the myocytes, which may prove toxic for the cells.<sup>8</sup> In animal models the drug has been shown to induce ventricular dysfunction, and at structural level cardiomyocyte enlargement and vacuolization have been observed, as well as mitochondrial pleomorphism, perivascular interstitial fibrosis and the induction of apoptosis.<sup>9</sup> Furthermore, proteasome inhibition generates changes in endothelial nitric oxide synthase (eNOS) activity and in nitric oxide levels—this in turn leading to vasodilatation and endothelial dysfunction associated with arterial hypertension and coronary disease, among other conditions. Other drugs are also under study, such as apremilast, which exerts a protective effect against carfilzomib-induced cardiotoxicity, and thus plays a key role in the modulation of oxidative stress.<sup>10</sup>

Oncohematological patients are fragile and require very complex management. Preventing serious adverse events in patients at risk though admission to intensive care for electrocardiographic and cardiorespiratory monitoring could prove necessary and constitute a new healthcare offer on

the part of ICUs. This would require the introduction of protocols involving multiple disciplines (Clinical pharmacology, Hematology and Intensive Care Medicine) in order to select those patients considered to be at high risk and who could benefit from such monitoring, in view of the limited number of ICU beds available.

**Table 1** Cardiovascular adverse effects of carfilzomib and cardiac toxicity risk factors.

Adverse events, percentage	Cardiac toxicity risk factors
<i>Cardiovascular</i>	
Cardiac arrhythmia (13.3%)	Previous cardiovascular disease
Heart failure (7.2–23%)	Combination treatment with doxorubicin
Coronary disease (3.4%)	Thoracic radiotherapy
Myocardiopathy (1.7%)	
Dyspnea (42.2%)	
<i>Hematological</i>	
Anemia (46.8%)	
Thrombocytopenia (36.3%)	
Neutropenia (20.7%)	
<i>Others</i>	
Pneumonia (12.7%)	
Serum creatinine elevation (24.1%)	
Acute renal failure (5.3%)	
Hyperglycemia (12%)	
Water-electrolyte alterations:	
hypopotassemia (14%),	
hypomagnesemia (14%),	
hypercalcemia (11%)	

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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## Serum gelsolin levels in aneurismal subarachnoid hemorrhage: Preliminary results



### Niveles séricos de gelsolina en pacientes con hemorragia subaracnoidea de origen aneurismático: resultados preliminares

*Dear Editor,*

Aneurismal subarachnoid hemorrhage (aSAH) is the most common cause of non-traumatic extravasated bleeding into the subarachnoid space and the main cause of sudden death from stroke.<sup>1</sup> Due to its high rate of mortality and morbidity, researchers have focused their efforts on improving clinical management, imaging techniques and identifying biomarkers that could early predict cerebral vasospasm, delayed cerebral ischemia and aSAH patients' outcome.<sup>2</sup> One of these biomarkers is gelsolin, a protein with a protective function: promotes the clearance of actin filaments released during tissue injury.<sup>3</sup> Its depletion has been related to poor outcome in various critical care pathologies.<sup>4</sup>

The aim of this preliminary study was to analyze gelsolin serum levels in patients with aSAH, describe its kinetic within 48 h post-bleeding and assess its role as a possible outcome predictor.

For this purpose, we included patients admitted to the NeuroCritical Care Unit (NCCU) at Virgen del Rocío University

Hospital in Seville, Spain, with the diagnosis of aSAH during a 5-month long period. The protocol, carried out in accordance with the Declaration of Helsinki, was approved by our hospital Institution Review Board. Written informed consent was obtained from patients family members. aSAH were eligible based on the following inclusion criteria: aged 18 or over, clinical history of SAH with evidence of bleeding on CT scan, NCCU admission within 24 h of onset, absence of tumor, trauma, previous episodes of SAH or any other neurological disease that could modify results. Clinical and demographic variables, collected prospectively, included: gender, age, Glasgow Coma Scale (GCS), Hunt and Hess (HH) classification, World Federation of Neurological Surgeons (WFNS) scale, Modified Fisher grade and 6-month mortality.

During the recruitment period, 15 aSAH patients fulfilled the inclusion criteria. Venous blood samples were collected on admission and 48 h after the bleeding. Additionally, a group of 10 healthy subjects were volunteers to extract a blood sample.

Serum gelsolin was measured using a double-antibody sandwich commercialized by Cloud-Clone Corp. (CCC, USA). Shapiro-Wilk normality test stated that gelsolin data followed a normal distribution. Hence, values were presented as means and standard deviation (SD). Comparison of means of quantitative variables between groups were made applying Student's *t* test. Correlation of gelsolin levels with other variables was assessed by Pearson's correlation coefficient. Statistical significance was defined as  $p < 0.05$ . Statistical analyses were performed using SPSS V20 software (IBM Inc., Chicago, IL, USA).