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Editorial

Rare Adverse Events: Establishing Causality

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ABSTRACT

3.5% of hospital admissions are due to an adverse reaction to a drug in developed countries. In addition, 10.1% of inpatients will present side effects to the pharmacological treatment administered.

Keywords: Adverse event, Causal association, Pharmacovigilance, Bortezomib, Phrenic nerve paralysis.

EDITORIAL

An adverse reaction[1] is considered rare when it has an incidence rate of less than 0.001[2]. Establishing a causal association between a rare adverse reaction and a drug is a difficult task that requires a multidisciplinary approach, and, hence, it is essential to discard other possible causes of sign or symptom development to establish a temporal relation between the onset of the symptoms and the time of administration of the drug, as well as to consult the information available in the literature regarding the safety of the drug. However, in many cases, there is no absolute certainty in this association at the time of presentation of the adverse effect. In this sense, applying algorithms to evaluate causality between drug and adverse reaction is a tool that can help detect this possible association.

We recently published a letter to the editor in Leukemia and Lymphoma which reports a rare and serious adverse reaction to subcutaneous bortezomib, causing bilateral phrenic nerve paralysis with secondary respiratory insufficiency and requirement of orotracheal intubation and mechanical ventilation[3].

Neuropathy is a well-known and widely reported toxicity of bortezomib[2,4]; however, involvement of the autonomic nervous system is an adverse reaction observed in less than 1% of patients treated with this drug[2,5]. Before the publication of this case, there was only one reference in the literature

describing phrenic nerve toxicity to bortezomib[6]. However, this is the first case with bilateral involvement of this nerve after subcutaneous administration of bortezomib, which causesgyhswe less neurotoxicity than the intravenous one[7,8].

In this patient, other possible causes that could be responsible for the symptomatology (the disease itself, amyloidosis, autoimmune diseases, etc.) were ruled out.

The fact that the neurotoxicity secondary to bortezomib is dose-dependent[2,3] and not idiosyncratic, made it difficult to establish a temporal relationship between administration of the drug and the adverse effect, since this occurred after several cycles of treatment. The physicians' knowledge of this circumstance, together with the fact that the patient presented mild peripheral neuropathy from the first cycle, allowed us to establish this temporal relationship.

Finally, the literature search of articles or clinical cases published and the application of the algorithm of Naranjo[9] obtaining a probable level of causality between the drug and the adverse reaction, allowed to establish the relationship between bilateral diaphragmatic paralysis and the administration of the drug.

Once this probable relationship was established, the drug was immediately interrupted with significant improvement in the patient's clinical condition, being extubated after a few days[3]. This evolution supported this causal association.

In pharmacovigilance, spontaneous reporting is the most commonly used system for identifying adverse drug reactions. Post-marketing surveillance allows detection of adverse reactions which were not observed in the clinical trial phase and, thus, contribute to the appropriate, rational, and safe use of drugs, as it constantly updates toxicity data and evaluates the benefit-risk balance of such drug in a larger population of patients[10].

Reporting clinical cases is another tool that helps to study and find out rare adverse reactions. The publication and consultation of these cases in the literature is very useful in clinical practice and can help health professionals to detect possible adverse drug reactions at an early stage.

The morbidity-mortality and the economic cost attributable to these adverse effects is very relevant and their early detection could have a positive impact on the patients' health and healthcare cost.

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