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Cardiotoxicity of antiemetic drugs in oncology: An overview of the current state of the art

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ABSTRACT

Purpose: Cardiac complications in cancer patients have been a significant medical problem in the last few years. Cardiosafety profile of most novel approved drugs, in cancer patients, is required by regulatory authorities. Risk of proarrhythmic effect associated with a new drug, in fact, is usually evaluated with specific studies conducted in agreement with ICHE14 guidelines. In this overview, we detailed the cardio safety profile of antiemetic drugs. In particular, we focused on data of 5HT3-RA drugs used for prevention of chemotherapy-induced nausea and vomiting in the oncology setting.
Methods: A literature search was conducted using the PubMed database to identify studies reporting arrhythmic complications of antiemetic drug used in oncology.
Results and conclusion: Most of the antiemetic drugs have been approved by regulatory authorities when ICHE14 guidelines were not issued, so the cardiotoxicity of those drugs has been defined with the post-marketing authorization pharmacovigilance activity. We reviewed the cardiotoxicity data of major antiemetic and adjuvant agents, providing a general overview and recommendations about their use in medical oncology.

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1. Introduction

Patients with advanced cancer are often exposed to multiple drugs that are used for the treatment of their disease, the associated complications (e.g. pain) and comorbidities (e.g. cardiovascular disease, diabetes, dyslipidemia), as well as for the prevention and treatment of the adverse events caused by cancer therapy (e.g. nausea and vomiting induced by chemotherapy and febrile neutropenia). This inevitably involves an increased risk of potentially harmful drug–drug interactions, which may be further complicated by reduced organ function (heart, liver, and kidney) typically seen in elderly patients, and particularly in cancer patients. A recent European multicenter analysis conducted in 11 countries in over 2000 patients who were taking opioid drugs to treat cancer pain has shown that more than one-fourth of patients were using 10 or more drugs. Approximately 45% of patients received unnecessary or potentially unnecessary drugs, and potential interactions showed to increase the risk of sedation, gastric ulcerations, bleedings, and neuropsychiatric and cardiac complications (Kotlinska-Lemieszek et al., 2014).

Cardiac complications in cancer patients have been a significant medical problem in the last few years (Salvatorelli et al., 2015). The complexity of treatment of cancer patients, the known cardiotoxic effects of both chemotherapeutic drugs and supportive therapy, as well as the increase in the mean life expectancy of the general population and cancer patients, have provided a clinical relevance to this issue (Salvatorelli et al., 2015; Bhave et al., 2014; Accordino et al., 2014).

Drugs can express their cardiotoxic potential either directly on myocardial muscle or by inducing a pro-arrhythmic effect through an inflammatory process that causes the development of arrhythmogenic foci, or by acting directly on cardiac conduction tissue (Bagnes et al., 2010). Blood hypertension states are frequently associated with the use of antiangiogenic agents, with a cardiotoxic effect resulting from hemodynamic changes and hypertension-related organ damage; this damage is also expressed in the kidneys, brain, and peripheral vascular circulation in general. Moreover, acute and chronic cardiac ischemic events can be observed, which are not necessarily related to a thrombotic coronary disease. Cardiotoxicity events and symptoms may occur both at an acute and a delayed phase and can be either transient or chronically persistent (Salvatorelli et al., 2015; Bhave et al., 2014; Accordino et al., 2014; Bagnes et al., 2010).

The current anticancer and supportive therapies often require complex and composite associations of different active principles. This obviously entails that, in order to evaluate their cardiotoxic potential, a mere description of the iatrogenic potential of each class of drugs is not sufficient, and that great attention should be paid to the potential (cardiotoxic) synergies between drugs of different classes (polypharmacy-based assessment) within the context of a multifactorial strategy (Salvatorelli et al., 2015).

Since 2005, the regulatory authorities have required that the risk of proarrhythmic effect associated with a new drug as a result of its direct action on heart conduction tissue should be evaluated in agreement with ICH E14 guidelines (Shah, 2005a,b) before the drug is marketed. The purpose of these guidelines is to evaluate a drug's liability to increase the QT interval as recorded in the electrocardiogram. The QT interval represents the duration of ventricular depolarization and subsequent repolarization and is measured from the beginning of the QRS complex to the end of the T wave. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of fatal cardiac arrhythmias, most clearly Torsade de Pointes (TdP), but possibly other ventricular tachyarrhythmias as well (Shah, 2005a,b). TdP is a rare and distinctive form of polymorphic ventricular tachycardia characterized by a gradual and progressive change in the amplitude and torsion of the QRS complex around the isoelectric line.

The QT interval is a measure of the time taken for ventricular depolarization and repolarization and is expressed as time units (usually milliseconds). Since QT interval is dependent on heart rate, in order to compare QT values over time at different rates, it is usually "corrected" (corrected QT interval or QTc) by estimating the value at an ideal heart rate of 60 b.p.m. using Bazett's formula (Bagnes et al., 2010).

Today, the effect of QT prolongation caused by some drugs and observed in the internal medicine setting is well known. In particular, this is true for cytotoxic agents, targeted therapies (Table 1) or clinical conditions (e.g. dystonia). It is known that some classes of new molecular agents, such as small molecule inhibitors of the intracellular tyrosine-kinase domain (e.g. vandetanib, pazopanib, nilotinib, lapatinib, sorafenib, cabozantinib, and sunitinib) are associated with QT prolongation and that their use should be closely monitored to prevent fatal arrhythmic events such as sudden cardiac death and TdP (Naing et al., 2012; Lenihan and Kowey, 2013). The use of drugs that prolong QT interval requires close monitoring/dose adjustment in patients with renal and/or liver function impairment, cardiovascular comorbidities, concomitant use of several drugs that potentially prolong QT interval, water-electrolyte imbalance or congenital long QT syndrome (Salvatorelli et al., 2015; Bhave et al., 2014; Accordino et al., 2014; Bagnes et al., 2010; Naing et al., 2012; Lenihan and Kowey, 2013).

The administration of targeted drugs often occurs in association with chemotherapeutic agents that are well known for their cardiotoxic effects (e.g. anthracyclines, taxanes, antimetabolites, etc.). However, less is known about the cardiotoxic profile of supportive therapies, which are almost invariably used in association with chemotherapy and/or targeted therapy and might contribute to creating synergies regarding cardiotoxicity (Bagnes et al., 2010). In the last few years, new information has become available about the cardiotoxic profile of supportive therapies; such information mainly comes from changes in the prescribing information of some products (e.g. ondansetron, dolasetron, metoclopramide), and from specific information from pharmaceutical companies (e.g. "Dear Doctor Letter") or regulatory authorities (e.g. FDA alerts, information notes from EMA or AIFA).

A category of mainstay drugs used in supportive therapy is that of antiemetics for the prophylaxis of nausea and vomiting. In the early 90's standard therapy for antiemetic prophylaxis were based on metoclopramide, haloperidol, prochlorperazine and/or steroids. Then, better control of emesis was obtained with the introduction of new agents such as 5-Hydroxytryptamine (3) receptor antagonists (5-HT3-RAs). In the last few years, the post-marketing experience with these drugs (e.g ondansetron) has shown that they are associated with a rare and difficult-to-quantify risk of acute arrhythmogenic events such as tachyarrhythmias, especially in the acute phase following intravenous (i.v.) administration, and QT prolongation (Brygger and Herrstedt, 2014). Therefore, it is essential for a medical oncologist to have a comprehensive knowledge of the cardiotoxicity risks associated with the antiemetic drugs. The aim of this overview is so to provide a current overview of the data about risk of QT prolongation with older and newest antiemetics agents commonly used for the prevention of chemotherapy-induced nausea and vomiting.

2. Methods

A systematic search of Pubmed was performed with the terms (palonosetron or granisetron or ondansetron or tropisetron or dolasetron or metoclopramide or aprepitant or olanzapine or dexamethasone or steroid or haloperidol or antiemetic or "5HT3