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Fluoropyrimidine-induced cardiotoxicity

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ABSTRACT

Fluoropyrimidines (5-fluorouracil and capecitabine) are antimetabolite drugs, widely used for the treatment of a variety of cancers, both in adjuvant and in metastatic setting. Although the most common toxicities of these drugs have been extensively studied, robust data and comprehensive characterization still lack concerning fluoropyrimidine-induced cardiotoxicity (FIC), an infrequent but potentially life-threatening toxicity. This review summarizes the current state of knowledge of FIC with special regard to proposed pathogenetic models (coronary vasospasm, endothelium and cardiomyocytes damage, toxic metabolites, dihydropyrimidine dehydrogenase deficiency); risk and predictive factors; efficacy and usefulness in detection of laboratory markers, electrocardiographic changes and cardiac imaging; and specific treatment, including a novel agent, uridine triacetate. The role of alternative chemotherapeutic options, namely raltitrexed and TAS-102, is discussed, and, lastly, we overview the most promising future directions in the research on FIC and development of diagnostic tools, including microRNA technology.

1. Introduction

The fluoropyrimidines 5-fluorouracil (5-FU) and capecitabine are antimetabolite drugs, widely used for the treatment of many cancers, including colorectal, breast, and head and neck malignancies.

5-FU is an analogue of uracil with a fluorine atom at the C-5 position in place of hydrogen. At cellular level, 5-FU is converted into three main active metabolites, such as fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate and fluorouridine triphosphate (FUTP), that are misincorporated into DNA and RNA and block biosynthetic processes through the inhibition of the nucleotide synthetic enzyme thymidylate synthase (TS) (Fig. 1) (Longley et al., 2003).

Capecitabine is the oral prodrug of 5-FU and it is converted to 5-FU inside tumor cells, rapidly absorbed through gastrointestinal mucosa and sequentially converted, via three metabolic steps, to 5-FU, resulting in higher intratumoral concentrations of 5-FU compared with normal adjacent tissue (Adjei, 1999). Other fluoropyrimidines, such as S1 (tegafur/glimeracil/oteracil) and UFT (tegafur/uracil), are available and are used as an alternative to 5-FU in some clinical circumstances (Adjei, 1999). 5-FU and capecitabine are generally well-tolerated, being myelosuppression, gastrointestinal and skin toxicity (hand-foot syndrome) the most common adverse events. Both drugs can also rarely induce cardiotoxicity, and the spectrum of cardiac effects is wide, including acute coronary syndromes, arrhythmias, heart failure, hyper- and hypotension, cardiogenic shock and sudden death (Polk et al., 2013).

The reported incidence of cardiovascular (CV) events varies greatly among different studies in patients treated with 5-FU or capecitabine (Table 1). The most frequently reported symptoms are chest pain, palpitations, dyspnea and hypotension (Polk et al., 2013).

The aim of our systematic review is to provide an updated overview of fluoropyrimidines-induced cardiotoxicity (FIC) and discuss new insight in its pathogenesis, detection and possible treatment options.

Abbreviations: 5-FU, 5-fluorouracil; BNP, brain natriuretic peptide; CK, creatinine phosphokinases; CK-MB, creatinine phosphokinases-myocardial band; CV, cardiovascular; DYPD, dihydropyrimidine dehydrogenase; ECG, electrocardiography; EF, ejection fraction; FAC, fluoroacetate; FBAL, α-fluoro-β-alanine; FIC, fluoropyrimidine-induced cardiotoxicity; FUTP, fluorouridine triphosphate; GLP-1, glucagon-like peptide 1; h-FABP, heart-type fatty acid-binding protein; hs-TnI, high-sensitivity troponin I; miRNA, microRNAs; Saβ-gal, senescence-associated β-galactosidase; S1, tegafur/glimeracil/oteracil; TnI, troponin I; TnT, troponin T; TS, thymidylate synthase; TST, treadmill stress test; UFT, tegafur/uracil; vWf, von Willebrand factor

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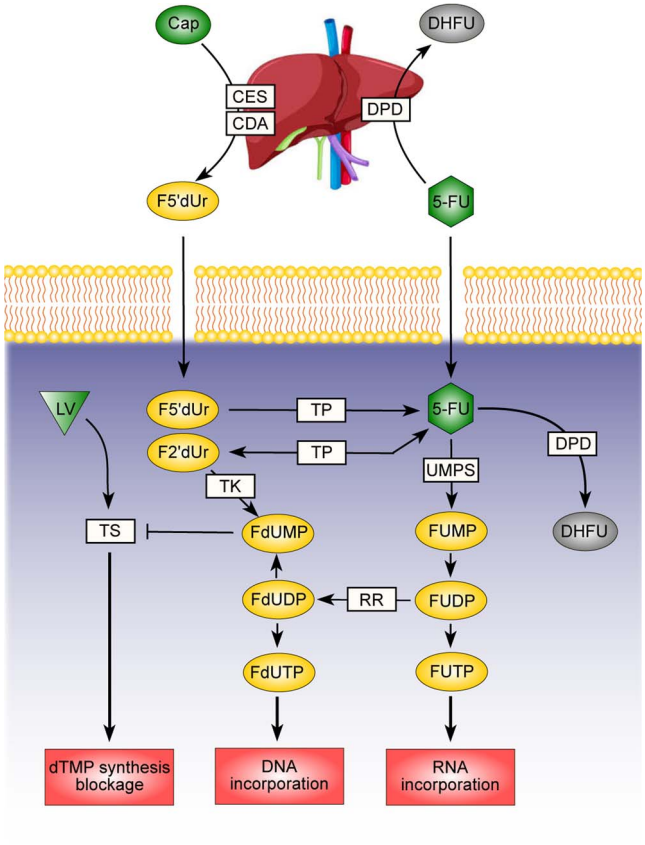

Fig 1. Activation of capecitabine and 5-fluorouracil. 5-fluorouracil and its prodrug capecitabine undergo a complex activating process, ultimately resulting in the production of three active metabolites, each determining a different damage to replicating cells.
Abbreviations;; 5-FU, 5-fluororuracil. Cap, capecitabine [*N*(4)-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine]. CES, carboxylesterase. CDA, cytidine deaminase. DHFU, dihydrofluorouracil (5,6-dihydro-5-fluorouracil). DPD, dihydropyrimidine dehydrogenase. dTMP, deoxythymidine monophosphate. F2'dUr, 5-fluoro-2'-deoxyuridine (floxuridine). F5'dUR, 5-fluoro-5'-deoxyuridine (doxifluridine). FdUMP, 5-fluorodeoxyuridine monophosphate. FdUDP, 5-fluorodeoxyuridine diphosphate. FdUTP, 5-fluorodeoxyuridine triphosphate. FUMP, 5-fluorouridine monophosphate. FUDP, 5-fluorouridine diphosphate. FUTP, 5-fluorouridine triphosphate. LV, leucovorin (folinic acid, 5-formyltetrahydrofolate). RR, ribonucleotide reductase. TK, thymidine kinase. TP, thymidine phosphorylase. TS, thymidylate synthetase. UMPS, uridine monophosphate synthetase (orotate phosphoribosyltransferase).

2. Material and methods

2.1. Search strategy

A structured search of PubMed database was performed to identify articles published in English in the last 17 years (1 st January 2000–30th April 2017), using the search terms: ((((((((((5 FU) OR 5 fluorouracil) OR fluoropyrimidine) OR capecitabine)) AND ((cardiotoxicity) OR cardiac toxicity))) OR ((((((5 FU) OR 5 fluorouracil) OR fluoropyrimidine) OR capecitabine)) AND ((((heart) OR cardiac) OR ischemia) OR arrhythmia)))) NOT anthracycline).

2.2. Study selection process

Two authors (ID and DM) independently screened and selected the articles by title and abstracts, excluding articles not relevant to the topic. The articles included in the final selection were categorized as: “review”, “prospective studies”, “retrospective studies”, “case reports” and “preclinical trials”.

2.3. Results of literature search and critical analysis of the results

Our search on PubMed database produced 583 results. We selected 162 articles and had them divided in five categories: 23 reviews, 10 retrospective studies, 22 prospective studies, 93 case reports and 14 preclinical trials.

We selected and analyzed mainly prospective trials and preclinical trials; retrospective studies, reviews and case reports were used to deepen specific issues, when necessary.

3. Pathogenesis

The pathogenesis of FIC has not yet been fully elucidated. Currently, several theories have been proposed, including vasoconstriction, endothelial injury leading to a procoagulant state and direct myocardial toxicity, all of which result in cardiac damage.

Fluoropyrimidines-induced coronary vasospasm and subsequent myocardial ischemia have historically been pointed out as the main pathogenic mechanism of cardiotoxicity based on several case reports and small preclinical trials (Karakulak et al., 2016; Kim et al., 2012; Mosseri et al., 1993).

Two clinical trials have prospectively validated this theory evaluating the effect of 5-FU infusion on brachial artery; using high resolution ultrasound the authors demonstrated a significant arterial vessel contraction after chemotherapy infusion (Salepci et al., 2010; Sudhoff et al., 2004). In Südhoff’s study pretreatment with nitrates prevented the brachial artery vasocontraction in patients who had previously experienced this event, further supporting the hypothesis of a direct effect of fluoropyrimidines on vessels’ musculature (Sudhoff et al., 2004).

A direct drug (or drug metabolite) damage to the vascular endothelium and to cardiomyocytes is considered another important mechanism of FIC. Different preclinical studies have observed an endothelial damage mediated by 5-FU resulting in endothelial and myocardial cells apoptosis. As a consequence, inflammatory pathway activation causes the release of vasoactive substances, platelets and fibrin accumulation with thrombi formation and increase of oxidative status in cardiocytes (Cwikiel et al., 1996; Durak et al., 2000; Tsibiribi et al., 2006).

Likewise, Eskandari et al. demonstrated that capecitabine as well causes damage in rat cardiomyocytes through oxidative stress, subsequent mitochondrial dysfunction and activation of apototosis (Eskandari et al., 2015).

A preclinical study conducted on both human endothelial cells and cardiomyocytes has shown that 5-FU has a direct effect on the proliferative capacity by blocking these cells in G1 and G2/M phases of the cell proliferation cycle (Focaccetti et al., 2015). Furthermore, this study confirms that 5-FU treatment induces oxidative stress, release of free radicals in cardiac cells and induction of senescence, with nuclear alterations, cytoplasmic vacuolization and membrane breakage, in agreement with other previous studies (Lamberti et al., 2014; Lamberti et al., 2012).

All these modifications finally result in triggering cells apoptotic programs and in direct CV damage.

Similar results were reached in another recent preclinical trial, where authors exposed endothelial cells to 5-FU or sera from patients taking capecitabine, showing an increase in the expression of the senescence-associated markers β-galactosidase (SA β-gal) and $p16^{INK4a}$, and a reduction in cell proliferation. Moreover, the authors proposed a possible protective role of glucagon-like peptide 1 (GLP-1) on cell senescence, providing a possible basis for future *in vivo* research (Altieri et al., 2017).

Spasojevic et al. analyzed the effect of 5-FU on erythrocytes, suggesting that it can induce modifications on erythrocyte membranes, causing structural alterations and functional changes, with a consequent decrease in oxygen levels in blood, leading to ischemia and