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Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: A systematic review of incidence, manifestations and predisposing factors

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ABSTRACT

Purpose: To systematically review the incidence, manifestations and predisposing factors for cardiovascular toxicity in cancer patients treated with systemic 5-fluorouracil or capecitabine.
Design: We searched PubMed, EMBASE and Web of science for studies with ⩾20 cancer patients evaluating cardiovascular toxicity of 5-fluorouracil and capecitabine. We hand searched the reference lists of all included studies. Study selection and assessment of risk of bias were performed by two authors independently.
Results: We identified 30 eligible studies (1 meta-analyses of 4 RCTs, 18 prospective and 11 retrospective). Symptomatic cardiotoxicity occurred in 0–20% of the patients treated with 5-fluorouracil and in 3–35% with capecitabine. The most common symptom was chest pain (0–18.6%) followed by palpitations (0–23.1%), dyspnoea (0–7.6%) and hypotension (0–6%). Severe clinical events such as myocardial infarction, cardiogenic shock and cardiac arrest occurred in 0–2%. Mortality rates ranged from 0 to 8%. Asymptomatic cardiac influence was demonstrated on ECG, in NT-proBNP measurements and with ultrasonic cyclic variation of integrated backscatter. Predisposing factors were mostly tested in univariate analyses. Preexisting cardiac disease was a risk factor in some studies, but there were divergent results. There was some evidence for increased cardiotoxicity during continuous infusion schedules and with concomitant cisplatin treatment. The effects of previous or current chest-radiotherapy were ambiguous.
Conclusion: Larger studies suggest an incidence of symptomatic cardiotoxicity of 1.2–4.3% during fluorouracil treatment, however subclinical cardiac influence are common. Possible risk factors are cardiac comorbidity, continuous infusion schedules and concomitant cisplatin treatment, but existing evidence are of insufficient quality.

Introduction

The antimetabolite 5-flourouracil (5-FU) is widely used alone or in combination regimens in the treatment of gastrointestinal, breast and head and neck tumours and its oral prodrug, capecitabine, is approved for treatment of colorectal cancer and metastatic breast cancer. Both 5-FU and capecitabine can induce cardiotoxicity in spite that capecitabine is activated preferentially in tumour cells. Fluorouracil cardiotoxicity presents during the course of chemotherapy and the spectrum of cardiac effects include acute coronary syndromes, arrhythmias, heart failure, hyper- and hypotension, cardiogenic shock and sudden death.[1,2]

The frequency and clinical manifestations of 5-FU-induced cardiotoxicity has been addressed in several studies during the last 4 decades. More recently, studies of cardiotoxicity from capecitabine have emerged. However, the reported frequency varies greatly in-between studies. It has been hypothesized that the wide variation in frequency and manifestations could be explained by differences in criteria for cardiotoxicity, differences in treatment schedules and differences in susceptibility of patients.[1,2] Hence, several attempts to identify potential predisposing factors for fluorouracil-induced cardiotoxicity have been made. Accurate estimation of the frequency of cardiotoxicity and identification of predisposing factors is important to identify patients at greatest risk and to guide safe application of these drugs. Therefore, we performed a systematic review of the incidence, manifestations and predisposing factors for cardiotoxicity from systemic 5-FU and capecitabine treatment in cancer patients. We stratified available evidence in: symptoms and clinical manifestations, electrocardiographic changes, changes in biomarkers and cardiovascular function assessed by imaging techniques.

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Methods

Search strategy

We searched PubMed (1966 – July 31, 2012), EMBASE (1980 – July 31, 2012) and Web of science (1900 – July 31, 2012) for publications in English on human using the search terms: (1) 5-fluorouracil OR 5-FU OR capecitabine; (2) ((Heart OR cardia* OR myocardi*) AND ischemia) OR arrhythmia; (3) cardiotoxi* (4) anthracycline [MeSH]. The final search combined #1 AND (#2 OR #3) NOT #4. Additionally we hand searched reference lists of retrieved papers.

Eligibility criteria

Studies were included if they met all following criteria: (1) $\geqslant$20 patients; (2) studies on patients with solid cancers; (3) treatment with systemic 5-FU-infusion or oral capecitabine as monotherapy or in combination with other chemotherapeutics; (4) studies reporting the frequency of cardiovascular toxicity. We excluded studies where cardiac medications were given prophylactic. If sequential upgrades on same study were published, we selected the most recent update.

Study selection process

All citations retrieved were reviewed on full citation, abstracts and indexing terms (where provided in the databases) by two authors independently (AP and DN). They were rated as "relevant", "possibly relevant" or "not relevant". Full-text publications of all potentially relevant articles were reviewed for eligibility independently by same two authors. All disagreements in rating or eligibility were resolved by discussion of the full-text articles till consensus was reached.

Data extraction

One author extracted the following data from all studies meeting eligibility criteria: The exact question addressed by the study, the number of patients enrolled in the study, dose, duration and mode of administration of 5-FU or capecitabine, name and dose of concomitant administered chemotherapeutic drugs, duration of follow up and cardiovascular profile of cohort participants at baseline. The outcomes of interest were cardiac adverse effects, mortality of likely cardiac origin and risk factors for cardiotoxicity.

Assessment of risk of bias

We graded studies as "randomised controlled trial" (RCT), "prospective study" (a priori fixed selection criteria) with or without a control group or "retrospective study" (of register data, medical charts etc.). We assessed the risk of bias within studies according to predefined criteria: (1) cohort consecutively sampled (selection bias); (2) adequate follow-up (attrition bias); (3) blinding of outcome assessors to treatment and duplicate outcome assessment (detection bias); (4) all pre-specified outcomes reported (outcome reporting bias); (5) adjustment for possible confounders i.e. cardiovascular co-morbidity and treatment with other potentially cardiotoxic drugs; (6) predefined criteria for outcomes measured; (7) systematically assessment of outcomes; (8) well-described patient characteristics. Point 1–5 evaluated internal validity and 6–8 external validity. Assessment of risk of bias was done at study-level by two authors (AP and DN). The risk of bias across studies was assessed graphically by plotting the incidence of cardiotoxicity and mortality in relation to study size (patient number).

Data synthesis

We summarised data using descriptive summary measures. We did not attempt a meta-analysis because of heterogeneity in design, eligibility criteria, treatment schedules, baseline patient characteristics and outcomes considered among studies.

Results

Results of literature search

The search strategy retrieved 1351 publications after duplicates were removed (Fig. 1). On the basis of full citation, abstracts and indexing terms 1313 publications were excluded. Of the remaining 38 publications, which were retrieved in full text for detailed examination, 31 met eligibility criteria. Hand searching the reference lists of retrieved papers identified one additional relevant publication. From the 32 papers 30 different studies were identified. One retrospective study (3) could include patients from cohorts of 3 prospective studies.[4–6] However, these studies did not evaluate the same types of outcome measure (symptoms, ECG changes, echocardiography etc.) and are therefore included in different sections of the review.

Description of the studies

The studies were published between 1978 and 2012 and were performed in 25 different reference centers (Table 1). Twenty-five studies investigated cardiotoxicity of 5-FU, two studies investigated cardiotoxicity of capecitabine and three studies included both patients treated with 5-FU and capecitabine. In total, 7973 patients were treated with 5-FU and 1386 patients were treated with capecitabine. Studies of 5-FU included a median of 68 (range 22–593) patients in prospective studies and a median of 346 (range 140–1350) patients in retrospective studies. Studies of capecitabine included a median of 153 (range 52–832) patients. Mean or median age of the patients ranged from 47 to 67 years. Most commonly, the site of primary cancer was gastrointestinal, breast or head and neck, however, in 9 studies of 5-FU patients with neuroendocrine, lung, prostate, cervix, pancreatic, hepatic, bladder or biliary tumours were included.

5-FU was administered as bolus infusion in 1766 patients, continuous infusion in 2432 patients and intermediate infusion in 461 patients, while the mode of administration was not reported for 3304 patients. 5-FU was given as a single agent to 1553 patients, in combination with other chemotherapeutics in 3303 patients whereas it was not reported for 3114 patients. Combination regimens varied extensively. The co-administered drugs included leucovorin, anthracyclines, oxaliplatin, cyclophosphamide, cisplatin, mitomycin, etoposide, interferon, paclitaxel, methotrexate, vincristine, peptichemio (a peptide complex of m-L-phenylalanine mustard), gemcitabine and irinotecan. Various dosing regimens for both 5-FU and co-administered drugs were used. Capecitabine was administered in doses of 1000–2500 mg/m^2/day as a 2-week on 1-week off regimen. It was either given as a single agent (1118 patients) or in combination (268 patients) with oxaliplatin, docetaxel, carboplatin, vinorelbine, irinotecan or lapatinib (only in 7 patients).

Baseline cardiovascular status of the patients varied extensively in-between studies of both 5-FU and capecitabine. The prevalence of patients with previous myocardial infarction or pre-existing cardiovascular disease ranged from 0% to 28% and risk factors for ischemic heart disease were present in 0–64% of the patients.