ELSEVIER

European Journal of Cancer 41 (2005) 1542–1546

European Journal of Cancer

www.ejconline.com

The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC)

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Received 19 April 2004; received in revised form 21 March 2005; accepted 21 March 2005
Available online 22 June 2005

Abstract

We examined the cardiotoxicity in 153 patients treated with capecitabine and oxaliplatin in two prospective trials for advanced colorectal cancer. Ten patients (6.5%) developed cardiac events. One patient (0.7%) had sudden death, one patient developed cardiac failure with raised troponin I while another developed ventricular tachycardia (VT). The remaining seven patients (4.6%) experienced angina and three of the seven patients had raised troponin I, one of which developed ventricular fibrillation. Eight events occurred within cycle 1 (median cycle 1 day 10). Four patients with angina and one patient with VT recovered on stopping capecitabine, four patients required additional medical management and the remaining patient died suddenly at home. Patients with ischaemic heart disease appeared to be at increased risk. Physicians and patients need to be aware of these complications, so that prompt discontinuation of treatment and appropriate interventions may be instituted.

Keywords: Capecitabine; 5-fluorouracil; Oxaliplatin; Cardiotoxicity; Thromboembolism; Angina; Ralitrexed

1. Introduction

The syndrome of cardiotoxicity associated with 5-fluorouracil (5-FU) is well known. It was initially described in 1975 [1], following which various case reports and studies have expanded on and attempted to shed more light on this syndrome. The incidence of cardiotoxicity reported in larger studies varies between 0.55% and 8.0% [2–6]. The spectrum of cardiac manifestations includes myocardial ischaemia, cardiomyopathy, left ventricular failure, arrhythmias, pericarditis and sudden death [3,7]. These studies are unsuitable for meta-analysis as they vary in design, 5-FU regimen, study population, period of evaluation and definition of cardiotoxic events. However, the notable trend is that the majority of events occur within the first cycle of chemotherapy and resolve with cessation of 5-FU. Angina is the most commonly reported symptom, and patients with a history of cardiac disease [2,6] or received infused 5-FU appear to be at greatest risk [3,4].

Capecitabine is an oral fluoropyrimidine, which is converted to 5-FU *via* a 3-stage process. This occurs preferentially in tumour cells and is thought to allow increased drug delivery to the tumour with reduced normal tissue exposure and toxicity [8–10]. Capecitabine is currently licensed for the treatment of colorectal and breast cancer and combination regimens with oxaliplatin have demonstrated comparable responses to infused 5-FU and oxaliplatin regimens [11–14]. Recent case reports of cardiac events associated with capecitabine

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doi:10.1016/j.ejca.2005.03.027

are similar to that seen with 5-FU [15,16]. A retrospective analysis of 1189 patients noted a 3% overall incidence and a 0.8% incidence of Grade 3 or 4 cardiotoxicity in patients receiving capecitabine monotherapy, with a similar incidence noted in the comparison arm receiving bolus 5-FU [17].

In view of the paucity of data on capecitabine-associated cardiotoxicity, we performed a toxicity analysis to evaluate the incidence and pattern of cardiotoxicity in patients treated with capecitabine and oxaliplatin for advanced colorectal cancer (CRC) at our institution. We have also attempted to identify potential risk factors involved in cardiotoxicity.

2. Patients and methods

2.1. Selection of patients

Patients were eligible if they were recruited into two trials (described below) before January 2004. This was to ensure that all patients had completed at least four cycles of treatment at the time of analysis. Eligible patients required a WHO performance status $\leqslant 2$, adequate bone marrow, hepatic or renal function. Patients with clinically significant cardiac disease, arrhythmias or angina pectoris were excluded. Patients with cardiac events were managed according to best clinical practice either at our institution or at their local hospital. A toxicity analysis was performed in April 2004 to determine the incidence of cardiotoxicity and thromboembolic events. Retrospective analysis of risk factors for ischaemic heart disease (IHD) was also performed.

2.2. Trial protocols

The first trial evaluated the efficacy and toxicity of pre-operative chemotherapy and chemoradiation in locally advanced rectal cancers. A 3 weekly regimen of capecitabine (1000 mg/m2/bd on day 1–14) and oxaliplatin (130 mg/m2/i.v. on day 1) was administered for four cycles prior to radiotherapy to the pelvis with concomitant capecitabine. Patients who were aged 75 years or older, received a reduced dose of capecitabine 750 mg/m2/bd and oxaliplatin 100 mg/m2. Patients with adequate response proceeded to surgery.

The second trial evaluated the same chemotherapy regimen for patients with metastatic colorectal cancer. Treatment was administered for a maximum of eight cycles. In patients with potentially resectable metastases, four cycles were administered pre- and post-operatively.

Both trials were undertaken with the approval of the local research ethics committee and patients' informed consent.

2.3. Data collection

The cardiotoxic and thromboembolic events were collected prospectively as part of toxicity assessment. Risk factors for IHD, patients' medications and confirmation of events were obtained from review of the medical notes. If patients received treatment for cardiac events elsewhere, details of the event were also obtained. Analysis did not include the period following surgery or radiotherapy. Pre-treatment electrocardiograms (ECG) were reviewed and where unavailable, documented results were used.

2.4. Data analysis

Recorded risk factors for IHD were smoking, diabetes, hypertension, hypercholesterolaemia and family history of IHD. Treatments with aspirin, warfarin, beta-blockers and calcium antagonists were also evaluated. These factors were analysed to determine whether they influenced the risk of cardiotoxicity and thromboembolism. Fishers exact test was used to compare differences in patient's characteristics.

3. Results

3.1. Study population

Between 2001 and 2003, 153 patients were recruited in the two studies. The characteristics of all patients and those with cardiotoxicity are listed in (Table 1). The median age was 63 years (range 33–81), 59% were men, 63% had metastatic disease and 31% of patients had previously received a 5-FU based regimen. Four patients (3%) had a history of IHD; 11 patients (7%) had other types of cardiac disease that included sick sinus syndrome, atrial tachyarrhythmia, aortic valve and rheumatic heart disease. Thirty-one patients (22%) had pre-treatment ECG abnormalities such as atrial fibrillation, conduction abnormalities, left ventricular hypertrophy, ST segment and T wave abnormalities. Sixty-eight patients (45%) had at least one risk factor for IHD.

3.2. Patients with cardiotoxicity

Ten patients (6.5%) developed cardiac events that are listed in (Table 2). One patient (0.7%) died suddenly on cycle 1 day 5 and post-mortem examination showed cardiac failure (CF) with triple vessel coronary disease. One patient developed CF with raised troponin I and ST segment depression, while another developed ventricular tachycardia (VT). The remaining seven patients (4.6%) experienced angina, three of these patients had a raised troponin I and one also developed ventricular fibrillation (VF). ECGs were performed in five of the seven