Capecitabine (Xeloda) as Monotherapy in Advanced Breast and Colorectal Cancer: Effectiveness and Side-effects


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Abstract. Background: Capecitabine (Xeloda) is a fluoropyrimidine which is transformed to 5-fluorouracil (5-FU) at the tumor site. The aim of the present study was to estimate the efficacy of this agent in pretreated patients with advanced breast and colorectal cancer, and to determine the response rate and adverse reactions. Patients and Methods: Forty-two patients (median age 65 years, range 27-80 years), 24 with breast cancer, 17 with colorectal cancer and one with a pancreatic islet tumor were included. Capecitabine was administered at a dose of 1200 mg/m2 twice daily for two weeks every 21 days. No other agent or supportive treatment was planned. Results: A partial response was observed in 29.16% of the patients with breast cancer and in 11.76% of the patients with colorectal cancer. Stable disease was observed in 58.33% and 70.59% of the breast cancer and colorectal patients, respectively. Adverse reactions were very mild with respect to myelotoxicity and GI tract toxicity. Grade 3 hand-foot syndrome was observed in three patients (7.14%). Hypertriglyceridemia, an unusual side-effect, was observed in 5/12 patients who were tested for serum cholesterol triglycerides. Conclusion: Capecitabine is a well tolerated treatment with low toxicity, rendering a partial response in 29.16% and 11.76% of patients with breast and colorectal cancer, respectively.

Capecitabine (Xeloda) is a fluoropyrimidine which is transformed to 5-fluorouracil (5-FU) at the tumor site. It is an orally administered enzyme-activated fluoropyrimidine carbamate, designed to generate high levels of 5-FU in tumor cells (1, 2). Capecitabine has been administered and has shown effectiveness mainly in advanced pretreated breast cancer patients. It has also been shown to be effective in patients with advanced colorectal cancer (3-6). Toxicity with this agent was mild and well tolerated. One adverse reaction that leads to the discontinuation of the administration of this drug is palmar-plantar erythrodysesthesia (hand-foot syndrome) which is not very common. Gastrointestinal side-effects are rarely seen (7-8). The aim of the present trial was to determine the effectiveness and toxicity of capecitabine monotherapy in pretreated advanced breast and colorectal cancer patients. Oral cytotoxic chemotherapy treatment has an advantage over intravenous administration as it can be applied without hospitalization, provided that toxicity is low.

Patients and Methods

The eligibility criteria included histological confirmation of the diagnosis, objective staging by imaging methods, bidimensionally measurable disease, prior treatment with established chemotherapy, a performance status (PS) of 0-2, expected survival of ≥12 weeks, adequate bone marrow reserve (leukocyte count ≥3,500/µl, platelet count ≥100,000/µl, hemoglobin ≥10 g/dl) and liver function (serum bilirubin ≤1.5 mg/dl and serum transaminases ≤3 times the upper normal limit [or ≤5 times the upper normal limit in cases of liver metastases]). This study was conducted with the approval of our Institutional Review Board and all patients gave their informed consent to participate.

Treatment plan. The patients were designated to receive a minimum of four courses of treatment and then to continue for eight or more courses unless there were inhibitory side-effects or disease progression. Capecitabine was given daily, orally for 14 consecutive days: two weeks of treatment, one week off treatment. One course was considered to be two weeks of treatment. The dose was 1200 mg/m2 twice daily and no supportive drugs such as antiemetics were programmed. Occasionally in cases of gastritis, antioxidants were supplied. The recommended dose is 1250 mg/m2 twice daily but our patients started at the 1200 mg/m2 x 2 dose, as the majority had had one or two series of prior chemotherapy. In cases of gastrointestinal (GI) side-effects, (grade 1) nausea/vomiting and diarrhea, the dose was reduced to 1 g/m2 x 2 daily. If the GI tract side-effects became intolerable, the treatment was stopped.

Baseline treatment assessment and evaluation. Before entry into the study all patients underwent the following evaluations: medical...
history, physical examination, tumor measurement or evaluation, ECOG performance status, ECG, full blood count, liver and renal function tests and urinalysis. Staging was determined by chest and abdominal computed tomography, bone scan and, occasionally, magnetic resonance imaging. Blood count, blood urea and serum creatinine were measured before each treatment and seven days after each course. Radiological tests were conducted after a current course of treatment if the clinical signs were indicative of disease progression.

**Definition of response.** Imaging-based evaluation was used for the assessment of response. A complete response (CR) was considered to be the disappearance of all measurable disease confirmed at four weeks at the earliest, and a partial response (PR) a 30% decrease of the tumor burden also at four weeks at the earliest after the completion of 4 courses of treatment. In stable disease (SD), neither PR nor progressive disease (PD) criteria were met and in PD, a 20% increase or more of tumor burden and no CR, PR or SD were documented before increased disease. Response data were based on the response evaluation criteria in solid tumors (RECIST) (9). A two-step deterioration in PS, a >10% loss of weight at pretreatment or increasing symptoms did not by themselves constitute progression of the disease, however, the appearance of these complaints was followed by a new evaluation of the extent of the disease. Only those responses maintained for at least 4 weeks were included and all were confirmed by an independent panel of radiologists.

**Trial design/criteria.** This was a single-center phase II study. The primary end-points of the study were response rate and tolerance, and the secondary end-point was survival. The duration of response was calculated from the day of the first demonstration of response until PD. The time to tumor progression (TTP) was calculated from the day of entry into the study until documented PD.

**Results**

**Patients’ characteristics.** From January 2003 until December 2005, forty-two patients were enrolled in this trial. The patients’ characteristics are shown in Table I. In addition to the 24 patients with breast cancer and 17 (11 male, 6 female) patients with colorectal cancer, one other patient had histologically confirmed inoperable islet tumor of the pancreas. The PS was 0-1 in the majority of patients and all patients were stage IV, with the exception of one of stage III (pancreatic tumor). Metastatic disease was present in the liver, lungs and soft tissue (for breast cancer). Thirteen patients were still alive at the end of the study.

**Compliance with treatment.** Treatment was given for up to 18 months with a median duration of 5 months. The number of courses was 202 (median 9, range 4-20). The median interval between treatment cycles was seven days. Five patients had a delay of two weeks each, due to gastrointestinal side-effects (diarrhea). The dose was reduced by 20% in 8 patients (three with vomiting). Treatment was stopped in three patients because of hand-foot syndrome.

**Toxicity.** All patients were evaluable for toxicity which is shown in Table III. Two patients had grade 1 neutropenia, five had diarrhea and three had nausea or vomiting. The dosage was reduced in these patients. Grade 3 advanced palmar-plantar erythrodysesthesia (hand-foot syndrome) was observed in three (7.14%) patients after at least six courses of treatment and treatment was stopped in these patients. In two other patients with minor (grade 1) hand-foot syndrome, the dose was reduced and treatment was postponed by two weeks, after which time they were able to continue treatment. No cardiotoxicity, nephrotoxicity, neurotoxicity or alopecia was observed.

In 5/12 patients tested for serum cholesterol triglycerides (TG), hypertriglyceridemia was detected. The measurement of lipids had not been planned initially, but was included after observation of one of the patients with breast cancer and liver metastases: before treatment this patient had had TG of 150 mg/dl which gradually increased to 1100 mg/dl within 6 months. She was taken off treatment for six weeks...
and her TG dropped to 200 mg/dl; when she resumed treatment, TG increased to 520 mg/dl. In the remaining four patients with elevated TG levels, the increase was 3-4 times higher than normal. No significant changes in other lipids were observed.

Discussion

Capecitabine (Xeloda) seems to be eligible for the treatment of advanced breast and colorectal cancer. Whether this agent should be given as monotherapy or in combination with other cytotoxic agents has not yet been clarified. There are studies that use capecitabine in combination with other agents (10, 11), but further evaluation is warranted. Capecitabine has several advantageous characteristics: toxicity is negligible in the great majority of patients and the treatment requires no hospitalization; also when given as monotherapy, it is unnecessary to do blood analyses more often than once a month. This is because there is no myelotoxicity when it is given as a single agent, as has been clearly shown by the present study. Only grade 1 myelotoxicity was observed in a very low percentage of patients. The responses to capecitabine were not very high, but taking into account that all of the patients had been pretreated, the 29% response rate in the breast cancer patients showed it to have some efficacy in advanced disease. In colorectal cancer the partial response was only 11.76% but with these patients disease stability (70.59%) can also be considered a valuable result. Similar results are described in another trial which showed a response rate and disease stability in 53% of the patient population (12). Another review study compared capecitabine and 5-FU and found the former to have superior effectiveness, with a statistically significant difference (13). This outcome combined with a reasonably good quality of life makes capecitabine a useful agent. The increase of serum triglycerides in a quite high percentage of patients who underwent the test for serum cholesterol triglycerides.

Hypertriglyceridemia was observed in 5/12 patients who underwent the test for serum cholesterol triglycerides.

References


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