Research Article

Low dose capecitabine is effective and relatively nontoxic in breast cancer treatment

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ABSTRACT

BACKGROUND: Capecitabine is widely used in breast cancer treatment, but the dose limiting toxicity is diarrhea, which can be severe or fatal. Much lower doses have been reported to be equally effective and less toxic.

METHODS: A retrospective chart review of patients treated from March 2012 through September 2013 in a single university-based medical oncology clinic was done to identify those with breast cancer who received 1000 mg p.o. of capecitabine daily. Toxicity was evaluated every 4 weeks using NCI common toxicity criteria 3.0 and effectiveness was evaluated every 4 weeks using RECIST criteria 1.1. Blood count was done every 4 weeks and blood chemistries and imaging as needed.

RESULTS: Twenty-three patients who received capecitabine 1000 mg daily and who returned for at least one subsequent visit were identified. Three patients had resected localized disease, 7 locally advanced disease, and 13 metastatic (stage IV) disease. Median age was 66 years (33-95). Most had received previous chemotherapy (median 3 agents). No toxicity more severe than grade 2 was seen. Two of these received concurrent treatment with trastuzumab and lapatinib, and one with low-dose weekly methotrexate. In the 16 patients with measurable disease who received capecitabine monotherapy, 9 partial responses were seen. Median duration of response was 5 months (2-15).

CONCLUSIONS: Continuous capecitabine 1000 mg daily appears to be effective in breast cancer treatment and has mild toxicity. A phase II study is needed to confirm these results. The drug could be used much more widely and safely if these results are confirmed.

KEYWORDS: breast cancer, capecitabine, toxicity, continuous, low-dose

INTRODUCTION

Capecitabine was approved in the United States for the treatment of advanced breast cancer in April of 1998 as monotherapy in patients with metastatic breast cancer 1) which was resistant to paclitaxel and to an anthracycline-containing regimen or 2) which was resistant to paclitaxel and for whom further anthracycline therapy was contraindicated. The dose approved was 1250 mg/m^2 twice daily on days 1-14 of a 21 day cycle, based on two previous single-arm phase II studies (1,2). The phase II studies defined the maximally tolerated dose, the standard dose utilized for drug development at that time. The same dose was subsequently approved for use in combination with docetaxel for patients with patients with metastatic disease who had received previous anthracycline therapy. In the monotherapy trials, 20% of patients had a complete or partial response to treatment, while 40%

Table 1. Patient characteristics by selection group

Characteristics	N
Biopsy-proven breast cancer	23
Extent of disease	
Resected early disease	3
Locally advanced disease	7
Distant metastases	13
Subtype of disease	
Luminal A	8
Luminal B	7
HER-2^{+}, ER/PR^{-}	1
Triple negative	7
Previous treatment	
Anti-HER-2 agents only	1
Hormonal agents only	2
Previous chemotherapy for adjuvant or advanced disease (3 also received anti-HER-2 agents)	20
3 previous drugs	13
4 previous drugs	4
5 previous drugs	3

experienced stable disease. Grade 3 or 4 diarrhea was seen in 14% of patients and grade 3 or 4 hand-foot syndrome in 10%.The median time to disease progression was 93 days. Multiple studies, reviewed by Naughton (3), showed that reduction in the daily dose or use on a variety of alternate schedules reduced toxicity without compromising efficacy. Doses in the 19 trials of capecitabine monotherapy reviewed by Naughton ranged from 1000-2650 mg/M2 daily or twice daily, given on either a continuous or intermittent schedule-, including 28 day, 7 day, 7 day-on/7 day-off, and 14 day-on/7 day-off cycles. Similar findings have been reported in several more recent trials (4,5). A formal dose-response study of the drug has not been reported in breast cancer nor in any other malignancy.

Based on the consistent observation of reduced toxicity with lower doses and with no diminution in efficacy, I elected to use the drug on a very low dose daily schedule to see if responses could be obtained without major toxicity. A daily schedule of administration was used to promote compliance. Lack of toxicity and observation of responses in the first few patients were gratifying, so the same low dose regimen was used in additional patients. Before receiving a prescription, each patient treated was informed that the dose used was lower than that customarily used, with less toxicity as well, and that I had observed responses in previous patients using the low dose schedule.

METHODS

This is a retrospective evaluation from a population of outpatients treated for breast cancer by the author at the Kirklin Clinic at the University of Alabama at Birmingham between March 2012 and September 2013. The records of each patient seen during that period were reviewed to identify patients who had received treatment with capecitabine. Three patients were excluded because they were found never to have taken the drug, even though prescriptions were given. One was excluded because she received the drug on a different schedule. Twenty-three patients were identified who received a prescription for capecitabine 1000 mg. p.o. daily on a continuous basis and who returned for at least one subsequent visit. When there was measurable or evaluable disease, response was evaluated using RECIST 1.1 criteria. Toxicity was evaluated using NCI common toxicity criteria 3.0. Complete blood count was done before treatment and at each subsequent visit; blood chemistries and imaging were done as clinically indicated. Both the review of all patients treated during this period and the specific review of the patients receiving capecitabine were approved by the Institutional Review Board of the University of Alabama at Birmingham.

RESULTS

Twenty-three patients were identified as described above who had taken capecitabine 1000 mg. p.o. daily and who returned for at least one follow-up outpatient visit. Patient characteristics are listed in table 1. The median age was 66 years (range 33-95 years). All were ambulatory with an ECOG performance status of at 0, 1, or 2.

Toxicity was mild, with no toxicity greater than grade 2. One patient had grade 2 nausea without vomiting, 1 grade 1 anemia, 2 grade 1 palmar irritation, 1 grade 1 diarrhea, and 1 patient had ongoing chronic disseminated intravascular coagulation with pre-existing cytopenias, all grade 2, which did not worsen

Table 2. Patient Responses

Responses	Number/ total
No measurable disease	4
Complete clinical response	1/19
Partial response	10/19
Stable disease	2/19 (3 and 9 months)
Increasing disease	6/19
Capecitabine monotherapy	
Partial response	9/16 (4 luminal A, 1 luminal B, 4 triple negative)
Stable disease	1/16 (3 months)
Increasing disease	6/16
Median duration of response	5 months (range2-15)
Median time to progression	3 months

during treatment. One patient died of hepatic necrosis and concurrent portal vein thrombosis after initial response to treatment. She presented with fatigue, increasing weakness, and dyspnea. The tumor in her breast and axillary nodes was little changed from the previous visit. Bilirubin was elevated at 5.7mg/dL; transaminases and alkaline phosphotase were also elevated. Prothrombin time was prolonged with an INR of 2.1; platelet count was decreased to 105,000/mm^3 while hemoglobin and white blood cell count were normal. D-dimer level was strikingly elevated at 19,295 ng/ml. The capecitabine was discontinued, since it was thought to be responsible for the liver abnormalities. Abdominal sonar showed changes consistent with fatty infiltration, but no evidence of metastasis; there was also a new pleural effusion and thrombosis of the portal vein. She was anticoagulated. Her liver tests worsened off capecitabine and the clot in her portal system enlarged. She died about 2 weeks later at home. I could not identify a report of a previous similar toxicity from capecitabine, and the manufacturer did not have a record of previous hepatic necrosis due to capecitabine either. Portal vein thrombosis, acute liver failure, and hepatic necrosis - all from clinically inapparent metastatic disease from breast cancer in the liver - have all been reported previously (6,7,8). In retrospect, she almost certainly died from hepatic failure due to progression of clinically inapparent liver metastases. The syndrome of acute liver failure due to clinically inapparent liver metastasis from breast cancer is well described in the series cited above by Mogrovejo et al (8).

Four patients did not have measurable disease and were evaluated only for toxicity. Two received concurrent trastuzumab and lapatinib, and one concurrent weekly oral methotrexate. Nineteen had measurable disease. The responses are summarized in table 2; the main point is that 9/16 patients treated with capecitabine monotherapy experienced a partial response to treatment, with a median duration of response of 5 months. Median time to progression was 3 months.

DISCUSSION

This early experience in a limited number of heavily pretreated patients suggests that capecitabine used on a daily schedule at a dose of 1000 mg. p.o., has very mild toxicity, and produces tumor shrinkage in some moderate proportion of patients. A formal prospective phase II study of capecitabine using this dose and schedule should be done to confirm these limited results. This represents less drug toxicity than has been observed on any previously reported drug schedule. The responses seen in the small number of patients in this series suggest no compromise in effectiveness. A prospective dose-response trial in patients with breast

cancer might be of interest, but no important differences in response rates to widely varying doses of the drug have been observed in multiple prospective trials, suggesting that there may be no advantage at all to a higher dose of capecitabine in patients with breast cancer. Lower doses yet could be tried, but the lack of any major toxicity observed here suggests little additional advantage for that. Capecitabine is widely utilized in other malignancies, especially gastrointestinal malignancies; dose-response trials in some of these might reveal comparable findings and would certainly be of interest.

If a prospective study confirms the findings of modest toxicity and preserved effectiveness of capecitabine used continuously at 1000 mg daily, that might well lead to expanded use of the drug. It could be combined with other chemotherapy agents and would be expected to improve response rates without adding important toxicity. Most newer cancer treatments involve molecularly targeted agents. At least some of these (transuzumab, for example) have modest activity as monotherapy but much higher rates of response when used with concurrent cytotoxic agents. Using low dose capecitabine with such targeted therapies would be of considerable interest, both in breast cancer and in other malignant diseases. Use of a relatively nontoxic but effective chemotherapy agent would also likely be suitable for frail or elderly patients in whom conventional chemotherapy would not be well tolerated.

ABBREVIATIONS:

ECOG, Eastern Cooperative Oncology Group;
ER, Estrogen receptors;
HER2, human epidermal growth factor receptor 2;
NCI, National Cancer Institute;
PR, Progesterone receptors;
RECIST,Response Evaluation Criteria in Solid Tumors

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