The Role of Capecitabine, an Oral, Enzymatically Activated Fluoropyrimidine, in the Treatment of Metastatic Breast Cancer

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Key Words. Capecitabine · Oral fluoropyrimidine · Thymidine phosphorylase · Breast cancer · Colorectal cancer · Taxane-resistant · Docetaxel · Paclitaxel

ABSTRACT

Capecitabine is an oral fluoropyrimidine that mimics continuous infusion 5-fluorouracil and generates 5-fluorouracil preferentially at the tumor site. It is activated via a three-step enzymatic pathway, the final step of which requires thymidine phosphorylase, an enzyme that is significantly more active in tumor than normal tissue. As an oral agent, capecitabine is more convenient for patients and medical personnel, and avoids the complications associated with venous access. This paper reviews the development and clinical experience of capecitabine in breast cancer treatment. Clinical trials have established the efficacy and tolerability of capecitabine in anthracycline- and taxane-pretreated metastatic breast cancer, showing that capecitabine is an effective therapy for patients who have exhausted all established treatment options. Moreover, randomized, phase II studies have demonstrated that capecitabine is effective in anthracycline-pretreated patients and as first-line therapy for metastatic breast cancer. In addition to its confirmed efficacy, the favorable safety profile of capecitabine, particularly the low myelosuppression rate, makes it an attractive agent for incorporation into combination regimens. Therefore numerous trials have assessed the feasibility of capecitabine-containing regimens, and have shown promising results. Capecitabine is an important new treatment option for breast cancer patients, and ongoing clinical trials should further define its role in a range of settings. The Oncologist 2001;6:56-64

INTRODUCTION

Breast cancer represents a major cause of morbidity and mortality for women in the Western world, with 175,000 new cases occurring in the U.S. every year. Approximately 50% of all patients treated with curative intent will develop metastatic disease, and the median survival time for patients after diagnosis of metastatic disease is 18-30 months. The treatment of patients who are resistant to hormonal therapy, are hormone-receptor negative, or have rapidly progressive visceral disease usually involves systemic cytotoxic chemotherapy. Primary goals of treatment in this setting are the relief of tumor-related symptoms, maintenance of quality of life, control of disease progression and, ultimately, prolonged survival with acceptable toxicity.

There is a need for convenient, well-tolerated, and effective agents for the treatment of patients with heavily pretreated metastatic breast cancer. The trend towards more aggressive treatment earlier in the disease course with agents such as paclitaxel or docetaxel, and the use of highly active agents in the adjuvant setting, have led to an increase in the number of patients presenting with metastatic disease that is resistant to or had failed taxanes and anthracyclines. Therefore, new therapeutic strategies are needed for these patients.

Capecitabine, a novel oral fluoropyrimidine, mimics continuous infusion 5-fluorouracil (5-FU) and generates 5-FU preferentially at the tumor site through exploitation of high intratumoral thymidine phosphorylase (TP) concentrations. Capecitabine has become an important treatment option for patients with metastatic breast cancer that has progressed following taxane therapy, and has shown promise in anthracycline-pretreated patients, as first-line monotherapy, and as a component of combination regimens. This paper presents an overview of the development and clinical experience of capecitabine in the treatment of metastatic breast cancer.

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RATIONAL DEVELOPMENT OF CAPECITABINE

Capecitabine was rationally designed as an orally administered, tumor-selective, fluoropyrimidine derivative. It was proposed that tumor-selective generation of 5-FU could potentially improve efficacy and safety by enhancing tumor drug concentrations and hence minimizing systemic exposure to 5-FU. To achieve this tumor selectivity, capecitabine was designed to exploit the tissue-specific localization of TP [1]. Following absorption through the gastrointestinal tract, capecitabine is first metabolized to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxylesterase in the liver (Fig. 1). 5′-DFCR is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase in the liver and tumor tissue. Finally, 5′-DFUR is converted to 5-FU by TP, which is significantly more active in malignant tissue than in adjacent healthy tissue. Therefore, the steps of conversion to 5-FU occur with increasing specificity for malignant cells. The cytotoxicity of capecitabine and its metabolites 5′-DFCR, 5′-DFUR, and 5-FU was studied in cultures of human cancer cell lines [1]. The investigators found that capecitabine and its metabolites 5′-DFCR and 5′-DFUR were not themselves cytotoxic, becoming active only after conversion to 5-FU.

Figure 1. Enzymatic conversion of capecitabine to 5-fluorouracil. CE = carboxylesterase; CyD = cytidine deaminase; 5′-DFCR = 5′-deoxy-5-fluorocytidine; 5′-DFUR = 5′-deoxy-5-fluorouridine; 5-FU = 5-fluorouracil.

PRECLINICAL STUDIES

The antitumor activity of capecitabine was confirmed in xenograft models of breast, colorectal, gastric, and cervical cancer cell lines (Fig. 2). Capecitabine was effective (defined as >50% growth inhibition) in 18 of 24 (75%) xenograft models [2]. In contrast, only 4% and 21% of tumors were sensitive to 5-FU and the oral fluoropyrimidine UFT (tegafur plus uracil), respectively. In the models tested, only capecitabine demonstrated the ability to inhibit tumor growth by more than 90%, and this level of inhibition was achieved in 29% of the xenograft models investigated. Capecitabine has also shown antitumor activity in 5-FU-resistant tumor lines [2, 3].

Further studies in xenograft models have demonstrated that capecitabine achieves tumor-selective generation of 5-FU. Following oral administration of capecitabine to tumor-bearing mice, tumor concentrations of 5-FU were 114- to 209-fold higher than in plasma [4]. The results of this preclinical study were recently confirmed in a clinical trial of colorectal cancer patients, which demonstrated that 5-FU is generated preferentially in tumors following oral administration of capecitabine [5]. The concentration of 5-FU in the primary tumor was on average 3.2 times higher than in adjacent nontumor tissue, and the mean 5-FU concentration in tumor tissue was 21 times higher than in plasma.

Preclinical studies have also demonstrated that sensitivity to capecitabine correlates with tumor concentrations of TP and, more particularly, with the tumor ratio of TP to dihydropyrimidine dehydrogenase, the enzyme that degrades 5-FU to noncytotoxic metabolites [2]. In contrast, the ability to predict response was not seen with UFT. This unique property of capecitabine may enable individualized treatment that would spare patients from unnecessary treatment and toxicity.

The role of TP in the conversion of capecitabine to 5-FU in tumor tissue offers the potential to further increase the efficacy of capecitabine through intratumoral TP upregulation. A number of cytotoxic agents, including taxanes, cyclophosphamide, and mitomycin C, are known to increase the activity of TP in tumor cells [6]. Human cancer xenograft studies of capecitabine in combination with paclitaxel and docetaxel have demonstrated striking synergistic antitumor activity in human breast cancer xenografts, with no increase in toxicity as measured by body weight [6]. Coadministration of taxanes with either 5-FU or UFT, however, led to only additive antitumor activity. Synergy has also been observed between capecitabine and other therapies that enhance TP activity, including cyclophosphamide and tumor irradiation [7, 8].

PHASE I STUDIES

A series of phase I dose-finding and pharmacokinetic studies was conducted to investigate capecitabine as monotherapy (two different schedules) or in combination...
with leucovorin. The maximum tolerated dose (MTD) of capecitabine was determined in three open-label, phase I studies in patients with solid tumors, predominantly breast and colorectal cancer. Capecitabine was administered either continuously [9] or intermittently (two-week treatment followed by a one-week rest period) [10], and in one study both schedules of capecitabine were administered in combination with leucovorin [11]. The MTD of continuous capecitabine was identified as 828 mg/m$^2$ twice daily, and the MTD for the intermittent regimen was determined as 1,500 mg/m$^2$ twice daily. When capecitabine was administered in combination with a fixed dose of oral leucovorin (30 mg twice daily), the MTD of continuous capecitabine was 502 mg/m$^2$ twice daily, and the MTD of intermittent capecitabine was 1,000 mg/m$^2$ twice daily for 14 days followed by a seven-day rest period.

**PHARMACOKINETICS**

After oral administration, capecitabine passes unchanged through the intestinal wall and is rapidly and almost completely absorbed [12, 13]. Maximum plasma concentrations of capecitabine and its metabolites are reached approximately 2 h following administration. A two-way, crossover study was conducted in patients with advanced colorectal cancer to investigate the influence of food intake on the pharmacokinetics of capecitabine. The investigators found that the influence of food intake on the pharmacokinetics of capecitabine and its metabolites varied considerably, but the effect on the area under the concentration time curve of 5′-DFUR and 5-FU was minimal with no impact on the apparent elimination half-lives of the metabolites [14]. It is recommended that capecitabine is administered with food as this was the procedure used in clinical trials.

Hepatic dysfunction is common in patients with liver metastases and therefore a study was conducted to investigate the effect of mild to moderate hepatic dysfunction caused by liver metastases (defined according to standard liver biochemistry tests: serum bilirubin, alkaline phosphatase, and transaminases) on the pharmacokinetics of capecitabine. No significant differences in the pharmacokinetics of capecitabine and its metabolites were observed in patients with mild to moderate hepatic dysfunction compared with patients with normal liver function [15]. Therefore, there is no need for a priori dose adjustment, although caution should be exercised when capecitabine is administered to patients with impaired hepatic function.

Another study has investigated the effect of the antacid Maalox® (containing aluminium hydroxide and magnesium hydroxide) on the pharmacokinetics of capecitabine [16]. Coadministration of capecitabine with Maalox® to patients with solid tumors did not affect pharmacokinetics of the three main metabolites (5′-DFUR, 5-FU, and FBAL), indicating that in patients treated with Maalox®, capecitabine can be administered as normal.

**PHASE II, DOSE-SELECTION STUDY**

The three capecitabine regimens identified in phase I trials were evaluated further in a randomized, phase II trial in advanced colorectal patients to select the most appropriate regimen for further clinical development [17]. The efficacy results are summarized in Table 1. Capecitabine was generally well tolerated in all three treatment arms, with no grade 3 or 4 myelosuppression, but toxicity was more pronounced in the leucovorin combination arm. Adverse events were characteristic of fluoropyrimidines (predominant grade 3/4 adverse events were diarrhea and hand-foot syndrome [grade 4 not applicable], and the majority were mild to moderate in intensity. Results of the study led to the selection by the investigators of the intermittent monotherapy regimen (1,250 mg/m$^2$ twice daily, days 1-14 followed by a seven-day rest period).

<table>
<thead>
<tr>
<th></th>
<th>Continuous capecitabine</th>
<th>Intermittent capecitabine</th>
<th>Capecitabine plus leucovorin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate (%)</strong></td>
<td>21 (9-36)</td>
<td>24 (11-41)</td>
<td>23 (10-40)</td>
</tr>
<tr>
<td><strong>Complete response (confirmed) (%)</strong></td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Partial response (confirmed) (%)</strong></td>
<td>15</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td><strong>Stable disease (%)</strong></td>
<td>51</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td><strong>Progressive disease (%)</strong></td>
<td>21</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Time to disease progression (months)</strong></td>
<td>4.2 (2.8-7.0)</td>
<td>7.5 (4.0-9.0)</td>
<td>5.4 (2.9-5.7)</td>
</tr>
</tbody>
</table>

*One patient withdrew consent prior to receiving medication.*
Metastatic Breast Cancer

Capecitabine in Taxane-Pretreated Patients

Until recently, there was no established treatment for patients with advanced, metastatic breast cancer that has progressed following anthracycline and taxane therapy. Therefore, there was an unmet medical need for effective and well-tolerated therapies for this patient population. A large, multicenter, single-arm, phase II trial was conducted to determine the efficacy and safety of capecitabine in patients with metastatic breast cancer that had progressed following paclitaxel therapy [18]. A total of 163 patients were enrolled into the trial, 162 of whom received treatment. All patients were heavily pretreated and had received two to three prior chemotherapy regimens (mean 2.5), one of which included paclitaxel. In addition, 91% had previously received anthracyclines, and 82% had received prior 5-FU. The mean number of prior chemotherapeutic agents was 4.7. Patients received oral capecitabine 1,255 mg/m² twice daily for two weeks followed by a one-week rest period, repeated in three-weekly cycles. The primary objective of the study was to demonstrate an objective response rate of at least 20%. Secondary endpoints included duration of response, time to disease progression, survival, and clinical benefit response (CBR).

The results clearly demonstrate that capecitabine is a highly active drug in the treatment of paclitaxel-pretreated metastatic breast cancer. In the 135 patients with measurable disease, the overall response rate was 20% with a complete response occurring in three patients. An additional 40% of patients achieved disease stabilization. The median duration of response was 8.1 months and the median time to disease progression was 3.0 months. Of the 27 responding patients with measurable disease, 63% had failed three prior chemotherapeutic regimens and 63% had received prior treatment with 5-FU. In a retrospectively defined subpopulation of 42 patients refractory to both paclitaxel and doxorubicin, the response rate was an impressive 29%.

The median overall survival for the entire patient population was 12.6 months. Median survival in the subpopulation of patients who responded to capecitabine had not been reached at the time of the data analysis (Fig. 3). In the patients who achieved disease stabilization, survival was similar to that of the responders, indicating that disease stabilization is a meaningful therapeutic outcome. The median survival of patients with stable disease was 12.8 months.

The reduction of tumor-related pain and the maintenance of patient quality of life are the principal treatment goals in the palliative setting. Therefore, an important secondary endpoint of this trial was assessment of CBR, a composite score of pain intensity, analgesic consumption, and performance status (Table 2). Among the 147 patients evaluable for CBR, the overall score was positive in 29 patients (20%) and stable in 45 patients (31%). In patients with positive responses, improvements in overall CBR lasted for more than 18 weeks. Of the 51 patients with considerable tumor-related pain at baseline (≥20 mm on a visual analog scale ranging from 0-100 mm), 47% experienced a durable 50% reduction in pain intensity with capecitabine treatment. In addition, 30% of patients with analgesic consumption ≥70 mg morphine equivalents per day reported a reduction in analgesic consumption. These data provide evidence that capecitabine alleviates tumor-related symptoms for patients with metastatic breast cancer.

The findings of this trial have been confirmed in a second multicenter trial involving 74 metastatic breast cancer patients. The design of the trial was similar to the first study described above, with the exception that patients pretreated with docetaxel were also eligible [19]. Capecitabine was administered according to the intermittent schedule, as described above. The response rate seen in the first trial was reproduced in this confirmatory study, with an overall response rate of 25% (95% confidence interval [CI] = 15%-36%). Similar response rates were observed in patients pretreated with paclitaxel or docetaxel (27% and 21%, respectively). The median duration of response was 8.3 months.

Table 2. Definition of positive clinical benefit response [18]

| Pain intensity | ≥50% reduction in patients with baseline pain ≥20 mm |
| Analgesic consumption | ≥50% reduction in patients with baseline analgesic consumption ≥70 mg morphine equivalents |
| Karnofsky performance score | Improvement of ≥20 points |

Figure 3. Survival in patients pretreated with paclitaxel: subgroup analysis [18].
with a median time to disease progression of 3.2 months. The median survival was 12.2 months (95% CI = 8.0-15.3 months). Of the 54 patients evaluable for overall CBR, scores were positive in 15% and stable in 41%. The efficacy findings, including the CBR data, are consistent with those seen in the paclitaxel-pretreated trial described above. Data from these 236 taxane-pretreated patients provide strong evidence for the antitumor and palliative efficacy of capecitabine.

**Capecitabine in Anthracycline-Pretreated Patients**

A randomized, phase II study evaluated capecitabine in patients with metastatic breast cancer that failed or were resistant to anthracycline treatment in the adjuvant or metastatic setting [20, 21]. Forty-four anthracycline-pretreated patients were randomized to receive either oral capecitabine (1,250 mg/m² twice daily intermittent regimen or 666 mg/m² twice daily continuous regimen) or paclitaxel (175 mg/m² on day 1 of each three-week cycle). The continuous capecitabine treatment arm was discontinued after the enrollment of only two patients because data from a phase II trial in colorectal cancer led to the selection of the intermittent regimen for further clinical development [17]. The study was continued with two treatment arms, but was prematurely terminated owing to inherent recruitment problems, with patients refusing randomization because of strong preferences for either an investigational oral therapy or an established intravenous regimen. Nevertheless, data from the 22 patients treated with intermittent capecitabine and the 19 patients treated with paclitaxel provide an indication of the efficacy and safety profile of capecitabine versus paclitaxel in anthracycline-pretreated patients. Objective tumor responses were observed in eight patients receiving intermittent capecitabine (36%; 95% CI = 17%-59%, including three complete responses) and five patients receiving paclitaxel (26%; 95% CI = 9%-51%, with no complete responses). The median time to disease progression was 3.0 months with capecitabine and 3.1 months with paclitaxel. Overall survival was also similar in the two treatment arms (median 7.6 and 9.4 months, respectively).

**Capecitabine as First-Line Therapy in Women Aged ≥55 Years**

A multicenter, randomized, phase II study evaluated capecitabine as first-line chemotherapy in older (≥55 years) metastatic breast cancer patients who had not received prior cytotoxic chemotherapy for their metastatic disease [22, 23]. Ninety-five patients were randomized in a 2:1 ratio to treatment with either intermittent capecitabine (1,255 mg/m² twice daily on days 1-14 followed by a seven-day rest period; n = 61) or intravenous CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-FU 600 mg/m² once every three weeks; n = 32). The median age was 69 years in the capecitabine arm and 70 years in the CMF arm. Patients receiving capecitabine achieved a response rate of 30% (95% CI = 18%-43%) compared with 16% (95% CI = 5%-34%) in the CMF arm. Complete responses were observed in 5% of patients treated with capecitabine and none of the CMF-treated patients. The median time to disease progression was 4.1 months in the capecitabine group compared with 3.0 months in the CMF group (Fig. 4). Median survival was 21.6 months versus 17.2 months, respectively.

This study showed that the benefit of capecitabine is not limited to the treatment of patients with heavily pretreated cancer. Two large, randomized, phase III trials have been designed to evaluate capecitabine as first-line therapy in patients with previously untreated metastatic breast cancer. The reference arm is CMF (Bonadonna schedule) in one of the trials and epirubicin/paclitaxel in sequence or in combination in the other trial. Another large, randomized, phase III trial of capecitabine in the adjuvant setting is planned by the Cancer and Leukemia Group B (CALGB) in older women with high-risk, node-negative, early stage breast cancer. This trial will compare capecitabine monotherapy with doxorubicin/cyclophosphamide or CMF, depending on the cardiac history of the patient.

**Capecitabine Combination Therapy**

Since the tumor-selective conversion of capecitabine to 5-FU is mediated by TP, the combination of capecitabine with agents that upregulate TP concentrations in tumor tissue offers the potential to improve efficacy further. The synergistic activity of capecitabine in combination with paclitaxel, docetaxel, cyclophosphamide, and radiotherapy has been demonstrated in preclinical studies, as discussed previously [6-8]. Therefore, phase I studies were conducted to investigate these combinations further. In a phase I dose-finding/pharmacologic study, 17 patients with solid tumors refractory to conventional therapy were treated with continuous capecitabine in combination with paclitaxel 135 or 175 mg/m² on day 1 of each three-week
cycle [24]. A regimen of continuous capecitabine 666 mg/m^2 twice daily and paclitaxel 175 mg/m^2 was recommended for further evaluation. No relevant pharmacologic interactions between the drugs were observed.

A second study evaluated the combination of intermittent capecitabine (either 825 or 1,000 mg/m^2 twice daily, days 1-14 followed by a seven-day rest period) in combination with paclitaxel (175 mg/m^2 as a 3-h infusion on day 1 of each three-week cycle). The study included 14 previously treated, paclitaxel-naive breast cancer patients [25] and showed that a regimen of intermittent capecitabine 825 mg/m^2 twice daily for 14 days in combination with paclitaxel 175 mg/m^2 on day 1 of a three-week treatment cycle is well tolerated. This regimen was recommended for phase II evaluation due to the promising efficacy demonstrated in the phase I trial, with 5 of 10 evaluable patients achieving a partial tumor response.

Capecitabine has also been evaluated as a combination partner for docetaxel. A matrix-designed, phase I trial identified two regimens suitable for phase II evaluation: intermittent capecitabine 825 mg/m^2 twice daily, days 1-14 plus intravenous docetaxel 100 mg/m^2 on day 1 of every three-week cycle, or intermittent capecitabine 1,250 mg/m^2 twice daily, days 1-14 plus docetaxel 75 mg/m^2 on day 1 of a three-week treatment cycle [26]. The latter regimen was selected for phase III evaluation in patients with metastatic breast cancer and recruitment is now complete for a trial comparing docetaxel 75 mg/m^2 plus intermittent capecitabine 1,250 mg/m^2 twice daily, with docetaxel 100 mg/m^2 alone.

Capecitabine has been investigated in combination with a number of other agents for the treatment of breast cancer. A phase I study in patients with advanced breast cancer has shown that a triple-drug combination regimen of capecitabine, docetaxel, and epirubicin is promising [27]. The principal dose-limiting toxicity was neutropenia and tumor responses were seen in 21 (91%) of 23 patients treated. Another phase I study showed that capecitabine plus vinorelbine combination therapy is well tolerated and clinically active in breast cancer patients [28]. The MTD has not yet been reached in this study, but objective tumor responses have already been seen in 15 (52%) of 29 evaluable patients treated at all dose levels, with only three grade 3/4 clinical adverse events reported.

**SAFETY IN CLINICAL TRIALS**

As well as assessment of the safety of capecitabine in each of the individual phase II trials described above, the safety profile of capecitabine has been evaluated using pooled data from a large population of 875 patients. Patients included in the analysis had received capecitabine for the treatment of metastatic breast cancer (n = 245) [18, 20, 22] or metastatic colorectal cancer (n = 630) [17, 29, 30]. All patients had a minimum follow-up of 3.0 months, with a median duration of treatment of 4.2 months. All trials used the National Cancer Institute of Canada Common Toxicity Criteria (version 1.0) to grade the severity of adverse events.

The most frequently reported clinical adverse events experienced by patients included in the safety population were hand-foot syndrome, diarrhea, and nausea (Table 3). Alopecia was very rare. The majority of treatment-related adverse events were classified as grade 1 (mild) or grade 2 (moderate) in intensity. There was a low incidence of grade 3/4 treatment-related clinical adverse events (Fig. 5). Grade 4 clinical adverse events occurred in only 3.4% of patients. Myelosuppression and blood chemistry abnormalities were rare (Table 4). The only grade 3/4 laboratory abnormality shift occurring in ≥5% of patients was hyperbilirubinemia, which was mainly an isolated event almost always affecting indirect bilirubin, and which was rarely associated with increases in other liver function abnormalities. Treatment-related deaths were rare (1.1%). These data confirm the results of the individual trials, and provide further evidence that capecitabine is a well-tolerated agent suitable for use in the outpatient setting.

In some patients receiving capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin, altered coagulation parameters and/or bleeding have been reported, and therefore these patients should be monitored carefully. Monitoring is also recommended in patients taking capecitabine concomitantly with phenytoin, as increased phenytoin plasma concentrations have been reported in some patients receiving these two agents concurrently.

**Table 3. Incidence of most common (≥10%) treatment-related clinical adverse events: overall safety population (n = 875)**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Incidence n of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot syndrome</td>
<td>457 (52.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>427 (48.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>371 (42.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>234 (26.7)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>213 (24.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>212 (24.2)</td>
</tr>
</tbody>
</table>

Figure 5. Incidence of treatment-related grade 3/4 adverse events: overall safety population (n = 875).
A dose modification scheme was used in all clinical studies, and was effective in avoiding recurrence of treatment-related adverse events. Of 319 patients treated with capecitabine in the four phase II clinical trials described above, approximately two-thirds did not require dose reduction. The most common causes of dose reduction in the remaining patients were diarrhea and hand-foot syndrome, but recurrence of adverse events following dose reduction was rare. Among patients who experienced grade 2-4 diarrhea or hand-foot syndrome, recurrence of the same adverse event at grade 3 intensity was reported in only 12% and 13%, respectively, and there were no grade 4 recurrences. In addition, in patients who required dose reduction for the management of adverse events, the efficacy of capecitabine in terms of response or time to disease progression was not reduced compared with patients receiving the starting dose of capecitabine throughout therapy [31].

The dosing schedule of capecitabine enables finer control of treatment compared with intravenous therapy, as during each cycle patients receive 28 separate doses of capecitabine, any of which can be withheld in the event of moderate toxicities. Therefore, an important approach in preventing toxicities is patient education and counseling. By educating patients to recognize and report early signs of toxicities and interrupt treatment as appropriate, development to more severe symptoms can usually be avoided.

**DISCUSSION**

Patients who have been heavily treated for metastatic disease present a particular problem as they are often symptomatic and have few treatment options. Further chemotherapy is of limited benefit because toxicity and diminished quality of life often outweigh gains from tumor regression. The ideal cytotoxic agent in the palliative setting offers a reasonable prospect of an antitumor response leading to a reduction in tumor-related symptoms with improved quality of life and minimal toxicity.

Capecitabine was rationally designed to provide an oral therapy that generates 5-FU preferentially in tumor tissue. An additional aim was to mimic continuous infusion 5-FU. Oral administration enables convenient, patient-oriented, home-based therapy, which most patients prefer to intravenous treatment administered in the clinic [32-34]. In addition, oral therapy avoids the problems and inconvenience associated with venous access.

Clinical trials have demonstrated that capecitabine is an effective treatment for metastatic breast cancer. Two large, multicenter, phase II studies including more than 230 patients have documented the activity of capecitabine in heavily pretreated patients who are refractory to or have failed treatment with anthracyclines and taxanes [18, 19]. In these strictly defined patient populations, capecitabine resulted in response rates of 20%-25%, with an impressive 29% response rate in a subpopulation of patients refractory to both paclitaxel and doxorubicin. Until recently, these patients had no established treatment, and therefore the approval of capecitabine by the U.S. Food and Drug Administration and the regulatory authorities of more than 35 countries worldwide represents an important advance in breast cancer treatment.

The benefit of capecitabine is not restricted to the treatment of heavily pretreated patients. Two randomized, phase II studies have demonstrated that capecitabine is effective both in anthracycline-pretreated patients [20] and as first-line treatment for metastatic breast cancer [22, 23]. Although these trials were not designed to demonstrate a statistically significant improvement in efficacy compared with paclitaxel or CMF, there was a trend towards improved response rates with capecitabine treatment.

Capecitabine is generally well tolerated, with a safety profile typical of infusional fluoropyrimidines. It is rarely associated with life-threatening adverse events and the most common toxicities in the safety population of 875 patients were hand-foot syndrome, diarrhea, and nausea. Alopecia and bone marrow suppression were rare with capecitabine treatment. Grade 4 clinical adverse events were infrequent (3.4%), and adverse events were manageable by treatment interruption and dose reduction, if necessary. A retrospective analysis of data from four clinical trials conducted in breast cancer patients [18-20, 22] indicated that in patients who began treatment at the recommended starting dose, dose reduction for adverse events did not have a negative impact on the efficacy of capecitabine [31].

Capecitabine has also shown promise in other solid tumors, particularly colorectal cancer. Two large, randomized, phase III trials have demonstrated that capecitabine is effective and well tolerated as first-line treatment for metastatic colorectal cancer, achieving superior response rates, at least equivalent time to disease progression and

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**Table 4. Incidence of grade 3/4 laboratory abnormalities: overall safety population (n = 875)**

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>Incidence n of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>21 (2.4)</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>19 (2.2)</td>
</tr>
<tr>
<td>Neutropenia/ granulocytopenia</td>
<td>30 (3.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (1.7)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>378 (43.2)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>31 (3.5)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>167 (19.1)</td>
</tr>
</tbody>
</table>

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CNS, central nervous system; CMF, cyclophosphamide, methotrexate, and fluorouracil; CMF, cyclophosphamide, methotrexate, and fluorouracil; Dox, doxorubicin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; HNC, head and neck cancer; LDM, leucovorin, docetaxel, and mitomycin; LTPA, leucovorin, tegafur, and potassium; 5-FU, 5-fluorouracil; OR, odds ratio; SD, standard deviation; T, taxol; WBC, white blood cell.
from home-based therapy, which can have important social implications, as well as improving patients’ feelings of control over their treatment. Capecitabine has shown a favorable safety profile with side effects typical of infusional fluoropyrimidines. Myelosuppression and alopecia are very rare, as are grade 4 adverse events (3.4%). Furthermore, patient education and counseling should enable patients to recognize early signs of toxicities before development to more severe adverse events.

Clinical trials are currently evaluating the efficacy and safety of capecitabine in the adjuvant setting and in combination regimens. These studies will further define the clinical role of capecitabine in breast cancer treatment.

CONCLUSIONS

Capecitabine is an oral agent that mimics continuous infusion 5-FU and generates cytoxic 5-FU preferentially at the tumor site. It is activated via a three-step enzymatic pathway, with the final step requiring TP, an enzyme that is significantly more active in tumor tissue than in healthy tissue. The novel mechanism of action of capecitabine results in high intratumoral concentrations of 5-FU while minimizing plasma concentrations of 5-FU.

Clinical trials have established the efficacy and tolerability of capecitabine as treatment for taxane-pretreated metastatic breast cancer, providing an effective treatment for patients who have exhausted all other established treatment options. As an oral agent, capecitabine is more convenient for patients, nurses, and physicians. Patients benefit from home-based therapy, which can have important social implications, as well as improving patients’ feelings of control over their treatment. Capecitabine has shown a favorable safety profile with side effects typical of infusional fluoropyrimidines. Myelosuppression and alopecia are very rare, as are grade 4 adverse events (3.4%). Furthermore, patient education and counseling should enable patients to recognize early signs of toxicities before development to more severe adverse events.

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NOTE ADDED IN PROOF

Since submission of this manuscript, results of a phase III trial comparing capecitabine and docetaxel with docetaxel alone in patients with metastatic breast cancer have been reported and show an improvement in response rate, progression free survival, and median survival with the combination regimen [35].

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