Single-Agent Capecitabine: A Reference Treatment for Taxane-Pretreated Metastatic Breast Cancer?

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ABSTRACT

The treatment of patients with metastatic breast cancer that has progressed despite previous anthracycline- and taxane-based therapy is a challenge for oncologists. Several agents, including vinorelbine, gemcitabine, pemetrexed, and particularly capecitabine, have been evaluated in this setting, either alone or in combination with other cytotoxic agents. The efficacy of many of these agents has not yet been clearly established in this setting, as the majority have been evaluated in a limited number of patients and predominantly in single-center trials. Furthermore, some agents with clinically meaningful activity are often associated with significant toxicity, particularly myelosuppression and neuropathy, while less toxic agents/regimens often exchange improved tolerability for reduced activity.

Capecitabine, an oral chemotherapeutic, is the agent that has been evaluated most extensively in this setting. A large, phase II trial (n = 163) conducted in North America demonstrated a disease control rate of 63%, including an objective response rate of 20%, median time to disease progression of 3.0 months, and median survival of approximately 1 year. Adverse events were typically mild to moderate in intensity and could be controlled with treatment interruption or, if necessary, dose adjustment to each individual’s tolerable dose. Data recently reported from three other large trials in taxane-pretreated patients have revealed similar efficacy and tolerability. Together, these four trials show that single-agent capecitabine, in a population of 500 patients, consistently produced clinically meaningful efficacy, including median survival of approximately 1 year, with a favorable safety profile. Myelosuppression and alopecia were particularly rare. In addition, the oral administration of capecitabine, which enables convenient, patient-oriented therapy, makes it an attractive treatment for patients. Based primarily on the results of the pivotal trial, capecitabine received regulatory approval as treatment for anthracycline- and taxane-pretreated (paclitaxel-pretreated in the U.S.) metastatic breast cancer. In light of the confirmatory results of subsequent large trials,
capecitabine is now considered a reference treatment in this setting, as no other agent has consistently demonstrated such high efficacy in as large a patient population.

INTRODUCTION

Anthracyclines have been established as a component of adjuvant and first-line chemotherapy for breast cancer. In patients whose tumors have progressed despite anthracyclines, the taxanes, docetaxel and paclitaxel, are often the next preferred treatment in this setting. In randomized trials, only docetaxel has demonstrated a significant survival advantage over other active regimens in patients with tumors in which prior anthracyclines have failed [1-4].

In an increasing trend toward more aggressive therapy earlier in the disease course, combinations of taxanes and anthracyclines are currently being evaluated as first-line chemotherapy for metastatic disease or as adjuvant therapy for primary breast cancer [5-9]. In the first-line setting, taxanes and anthracyclines are associated with response rates in the range of about 20%-40% as monotherapy to as high as 80% for combination regimens in selected patient populations [10].

The increasing use of taxanes and anthracyclines earlier in the disease course means that clinicians are now more frequently faced with the challenge of treating patients with disease that is resistant to these highly active agents or who are not candidates to receive them because of associated cardiotoxicity. In this context, optimal palliation, maintenance of quality of life, and minimal interference with a normal lifestyle are particularly important. Thus, an ideal cytotoxic treatment in this setting should offer a reasonable prospect of response with minimal toxicity, reduce tumor-related symptoms, enhance or maintain performance status, maximize progression-free survival, be suitable for convenient administration in an outpatient environment, and ultimately, prolong overall survival.

SINGLE-AGENT THERAPEUTIC OPTIONS FOR PATIENTS WHOSE DISEASE HAS PROGRESSED POST TAXANE THERAPY

A number of investigational approaches have been evaluated in patients with anthracycline- and taxane-pre-treated metastatic breast cancer (Table 1) [11-30]. Most of the studies have been small phase II trials (fewer than 50 patients) or retrospective subpopulation analyses.

<table>
<thead>
<tr>
<th>Chemotherapeutic agent(s)</th>
<th>Response rate % (95% confidence interval)</th>
<th>Median duration of response (months)</th>
<th>Median time to progression (months)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (n = 46) [11]</td>
<td>17 (8-33)</td>
<td>6.7</td>
<td>2.3</td>
<td>10.5</td>
</tr>
<tr>
<td>Paclitaxel (96-hour infusion) (n = 26) [12]</td>
<td>27 (12-48)</td>
<td>6.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vinorelbine (every 2 weeks) (n = 14) [13]</td>
<td>29</td>
<td>NA</td>
<td>2.8</td>
<td>NA</td>
</tr>
<tr>
<td>Vinorelbine (SD) (n = 14) [14]</td>
<td>0 (0-23)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vinorelbine (weekly) (n = 40) [15]</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
<td>6.0</td>
</tr>
<tr>
<td>Vinorelbine (HD with G-CSF) (n = 40) [16]</td>
<td>25 (13-41)</td>
<td>NA</td>
<td>3.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Gemcitabine (n = 23) [17]</td>
<td>0 (0-15)</td>
<td>NA</td>
<td>1.9</td>
<td>7.8</td>
</tr>
<tr>
<td>5-FU (CI) (n = 35) [18]</td>
<td>12 (3-27)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pemetrexed (n = 32) [19]</td>
<td>19 (7-36)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pegylated liposomal doxorubicin (n = 151) [20]</td>
<td>NA</td>
<td>NA</td>
<td>2.9</td>
<td>10.4</td>
</tr>
<tr>
<td>5-FU (CI) + vinorelbine (n = 37) [21]</td>
<td>62</td>
<td>NA</td>
<td>6.0</td>
<td>13.0</td>
</tr>
<tr>
<td>5-FU (CI) + oxaliplatin (n = 64) [22]</td>
<td>27</td>
<td>NA</td>
<td>4.8</td>
<td>11.9</td>
</tr>
<tr>
<td>5-FU/LV (CI) + cyclophosphamide (n = 41) [23]</td>
<td>27 (13-40)</td>
<td>8.0</td>
<td>9.5</td>
<td>13.0</td>
</tr>
<tr>
<td>Gemcitabine + irinotecan (n = 36) [24]</td>
<td>22 (6-37)</td>
<td>5.5</td>
<td>7.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Gemcitabine + cyclophosphamide + 5-FU/LV (n = 46) [25]</td>
<td>37 (23-51)</td>
<td>NA</td>
<td>6.0</td>
<td>NA</td>
</tr>
<tr>
<td>Gemcitabine + cisplatin (n = 28) [26]</td>
<td>39 (22-59)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Gemcitabine + vinorelbine (n = 31) [27]</td>
<td>22</td>
<td>6.0</td>
<td>3.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Gemcitabine + vinorelbine (n = 29) [23, 28]</td>
<td>48 (29-67)</td>
<td>4.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Eniluracil/5-FU (n = 44) [29]</td>
<td>16</td>
<td>5.4</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Eniluracil/5-FU (n = 84) [30]</td>
<td>10 (4-18)</td>
<td>4.6</td>
<td>2.3</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Abbreviations: CI = continuous infusion; SD = standard dose; HD = high dose; 5-FU = 5-fluorouracil; LV = leucovorin; NA = not available.
Significant efficacy was reported in two studies investigating taxane crossover. In the first of these, paclitaxel 120-140 mg/m², was administered over 96 hours every 21 days to patients pretreated with taxanes, predominantly docetaxel [12]. The response rate was 27%, grade 4 neutropenia was reported in 61% of patients, and grade 3/4 stomatitis was seen in 15% of patients. Time to disease progression and overall survival were not reported. Similarly, in the second of these studies, docetaxel 100 mg/m², administered on day 1 of a 21-day cycle to patients previously exposed to paclitaxel resulted in a response rate of 17%, and overall survival was more encouraging than in most other trials (median, 10.5 months). Grade 4 neutropenia was reported in 72% of patients, with febrile neutropenia in 24% of patients [11].

Vinorelbine has been extensively studied in patients with taxane-pretreated disease. High-dose (30-35 mg/m² weekly) vinorelbine was active in one study, with an objective response rate (ORR) of 25%, but was associated with dose-limiting myelosuppression (grade 3/4 neutropenia in 58% of patients) and required concomitant G-CSF support [16]. At a dose of 20 mg/m² every 2-3 weeks, vinorelbine was better tolerated but yielded a 0% ORR [14]. In another study, the planned dose of vinorelbine was reduced from 30 mg/m² to 25 mg/m² weekly after the first 6 of 40 patients were enrolled. An ORR of 25% was obtained [15].

Other single agents that have been investigated include gemcitabine and pemetrexed. Gemcitabine (1,200 mg/m² on days 1, 8, and 15 of a 28-day cycle) was largely ineffective as reported in a study by Smorenburg et al. [17], with a 0% response rate. Moreover, the median time to disease progression was very short (1.9 months), as was median overall survival (7.8 months). Other investigators have reported response rates of 12%-30% with gemcitabine in anthracycline- and taxane-pretreated patients [31-33]. The investigational agent pemetrexed (500 mg/m² every 21 days), an inhibitor of several folate-dependent enzymes, produced a tumor response in 5 of 33 patients (15%), with grade 3/4 neutropenia reported in 29% of patients and grade 3/4 skin toxicity in 10% of patients [19].

**Combination Therapies for Patients Whose Disease Has Progressed Post Taxane Therapy**

In an attempt to improve treatment options, combination regimens including some of the agents with limited or no single-agent activity in this setting have also been evaluated in small phase I/II trials (Table 1). For example, in a trial including 37 patients pretreated with anthracyclines and taxanes, vinorelbine 25 mg/m² on days 1 and 5, plus infused 5-fluorouracil (5-FU) 500 mg/m² on days 1-5 of a 21-day cycle, produced a response rate of 62%, independent of previous response to anthracycline/taxane treatment [21]. The median time to disease progression was 6 months, and median overall survival was 13 months. However, toxicity was significant, with febrile neutropenia occurring in 14% of patients [21]. In another trial in 64 patients, oxaliplatin (130 mg/m² on day 1 of a 21-day cycle) in combination with infused 5-FU (1,000 mg/m² on days 1-4) induced a response in 27% of patients [22]. The combination was associated with an incidence of grade 3/4 neutropenia of 35%. Other combination regimens evaluated in small phase I/II trials are summarized in Table 1. Of note, many of these regimens incorporated protracted infusion of 5-FU, which requires central venous access and is associated with a certain inconvenience to patients.

Until the regulatory approval of capecitabine, no standard reference therapy existed for anthracycline- and taxane-pretreated patients. The benefit of using combinations of agents is questionable in the second- or third-line, palliative setting because of greater toxicity.

**Oral Capecitabine**

Capecitabine (Xeloda®) is a novel, oral fluoropyrimidine carbamate, which was rationally designed to generate 5-FU preferentially in tumor tissue and mimic continuous infusion 5-FU. The oral administration of capecitabine is an attractive feature: treatment at home is associated with improved quality of life in patients with advanced cancer [34], and patients are known to prefer oral to i.v. therapy, as demonstrated in two studies.

In the first of these studies, interviewers used a structured questionnaire to determine the preferred route of administration in 103 patients with advanced cancer scheduled to undergo palliative treatment [35]. The strength of preference and potential factors that might influence their choice were evaluated, and patients were asked whether they would accept lower efficacy to retain their chosen route of administration. In total, 89% of patients preferred oral therapy. Major reasons for this preference were convenience (57%), problems with i.v. lines or needles (55%), and a better environment for administration of chemotherapy (i.e., the home) (33%). However, ≥70% patients were not prepared to sacrifice efficacy (in terms of either response rate or duration of response) to retain their preference.

In the second of these studies, patient preference for oral or i.v. treatment was investigated in a randomized, crossover trial comparing an oral fluoropyrimidine regimen with i.v. 5-FU/leucovorin therapy in patients with advanced colorectal cancer [36]. Patients were randomly assigned to one cycle of oral therapy followed by one cycle of i.v. therapy or vice versa, thus acting as their own controls. Using a questionnaire-based approach, patient preference and reasons for preference were assessed before treatment and again after...
receiving both cycles of treatment (without knowledge of tumor response). Of 31 evaluable patients, the majority (84%) preferred oral therapy. For those patients who preferred oral therapy, the most important treatment features recorded after treatment administration were that no i.v. access was required (i.e., that the drug was a pill) and that the drug could be taken at home. The order in which patients were exposed to therapy did not influence patient preference.

The evidence supporting the use of capecitabine in patients with metastatic breast cancer who have been previously exposed to taxanes has been provided by four large trials, described below.

**CAPECITABINE IN TAXANE-PRETREATED PATIENTS**

Capecitabine is the most extensively evaluated agent in taxane-pretreated metastatic breast cancer. Five hundred patients have been enrolled in four large, multicenter clinical trials (Tables 2 and 3) [37-40], and these studies have shown consistent efficacy and safety data.

The pivotal phase II trial was conducted in women with paclitaxel-refractory metastatic breast cancer at 24 medical centers in North America (Table 2) [37]. All patients had tumors that had progressed despite adequate paclitaxel treatment for metastatic disease. Oral capecitabine was administered at the standard dose of 1,250 mg/m² twice daily for 14 days, followed by a 7-day rest period.

Of the 163 patients who entered the study, 162 received capecitabine and were included in the analyses of efficacy and safety. The study population represented a poor prognostic group: 75% of patients had more than two metastatic sites at baseline, and visceral metastases were present in 68% of patients. All patients were heavily pretreated: 100% had received prior paclitaxel, 91% had received prior anthracyclines, and 82% had received prior 5-FU-containing therapy (usually as an i.v. bolus) (Table 2). The mean number of prior chemotherapeutic regimens was 2.5, and the mean number of prior chemotherapeutic agents was 4.7.

Capecitabine demonstrated activity in this heavily pretreated population. The ORR was 20%. An additional 43% of patients achieved stable disease, giving a disease control rate (complete or partial response or stable disease) of 63% (Table 3). The median duration of response was 7.9 months,
and the median time to disease progression was 3.0 months. Median survival after 143 events, as reported in a recently presented update of this study, was 11.6 months [41]. A subgroup analysis demonstrated that overall survival in patients with stable disease was similar to that in patients achieving an objective response (Fig. 1), indicating that stable disease is a clinically meaningful outcome. Among the 51 patients with significant pain at baseline, 47% experienced durable pain relief.

A number of confirmatory studies have evaluated single-agent capecitabine in patients whose disease has progressed during or following treatment with either paclitaxel or docetaxel (Table 2). The patients in these studies, as in the pivotal study, were heavily pretreated and similar in terms of age, performance status, and distribution of metastatic sites. In all of these studies, capecitabine was administered according to the standard intermittent dosing schedule (1,250 mg/m² twice daily, days 1-14 every 21 days).

Efficacy data in the three confirmatory trials confirm the high activity of capecitabine in taxane-pretreated patients, as shown in Table 3. Between 54% and 62% of patients achieved disease control, and the median duration of response ranged from 5.0 to 8.3 months. Median time to disease progression was approximately 4.0 months and, as with the pivotal, U.S. study, median overall survival was approximately 1 year (Fig. 2).

These results, therefore, confirm the significant efficacy observed in the pivotal study in patients with paclitaxel-pretreated disease [37, 41] and demonstrate that capecitabine is an effective therapy for patients who have received prior treatment with docetaxel.

The safety profile of capecitabine in taxane-pretreated metastatic breast cancer

In all four trials, capecitabine demonstrated a favorable safety profile, characteristic of infused fluoropyrimidines (Fig. 3). The predominant adverse events were cutaneous (hand-foot syndrome affecting the palms and soles of the hands and feet) and gastrointestinal (nausea/vomiting, diarrhea, stomatitis). Adverse events were typically mild to moderate in intensity and could be controlled with treatment interruption and dose adjustment to each individual’s tolerable dose, as described later in this article. There was no evidence of cumulative toxicity, and the incidence of grade 3/4 adverse events per treatment cycle was low. Clinical grade 4 adverse events occurred in 2% of patients, and there were no treatment-related deaths. Diarrhea and
hand-foot syndrome (occurring in 12% and 15% of patients, respectively) were the two treatment-related adverse events that occurred with grade 3/4 intensity in more than 10% of patients. Myelosuppression was particularly rare, as was hair loss.

**PRACTICAL PATIENT MANAGEMENT WITH CAPECITABINE**

All phase II/III trials of capecitabine have included a standard dose modification scheme, involving treatment interruption, in the event of grade 2 or more severe toxicities, and dose reduction (Table 4). The aims of dose modification are to prevent the development of more severe toxicities and avoid the recurrence of toxicities, while maintaining efficacy at an individually adjusted dose level.

As an oral agent, capecitabine therapy can easily be interrupted at the first onset of a grade 2 or more severe toxicity. Twice-daily dosing provides 27 opportunities per cycle to interrupt capecitabine therapy if required.

At the standard single-agent capecitabine starting dose of 1,250 mg/m² (given on days 1-14 in a 21-day cycle), between one-third and one-half of patients require dose reduction. For example, in the pivotal U.S. trial, 33% of patients required dose reduction [41]. The median time to dose reduction in that study was 1.5 months, equivalent to approximately two cycles of treatment.

The dose modification scheme was very effective in controlling the recurrence of adverse events associated with capecitabine. As shown in Figure 4, the key toxicities of capecitabine (diarrhea, hand-foot syndrome, and stomatitis)

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**Table 4. Capecitabine dose modification scheme**

<table>
<thead>
<tr>
<th>NCIC CTC toxicity grade</th>
<th>Appearance</th>
<th>Action</th>
<th>Adjustment for next dose (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>First</td>
<td>Interrupt</td>
<td>100%*</td>
</tr>
<tr>
<td></td>
<td>Second</td>
<td>Interrupt</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Third</td>
<td>Interrupt</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Fourth</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>First</td>
<td>Interrupt</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Second</td>
<td>Interrupt</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Third</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>First</td>
<td>Interrupt</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Second</td>
<td>Discontinue or interrupt</td>
<td></td>
</tr>
</tbody>
</table>

*Clinical trials are investigating capecitabine dose reduction to 75% at the first appearance of a grade 2 side effect

bAt the discretion of the physician.

Abbreviation: NCIC CTC = National Cancer Institute of Canada Clinical Trials Group.
were markedly reduced following dose reduction [41].

Importantly, the efficacy of capecitabine appears to be maintained following dose modification in patients who begin treatment at the standard dose. A retrospective analysis conducted to evaluate the impact of dose modification on efficacy demonstrated that risk of disease progression was no greater in patients requiring dose reduction for adverse events than in those not requiring dose reduction (hazard ratio 0.987; p = 0.940) [41].

In order to effectively implement the dose modification scheme and, thus, manage side effects, patient education is essential, as with all oral, outpatient cancer therapy. All patients prescribed capecitabine should be educated to recognize its side effects and their severity. They should be instructed to interrupt their treatment if moderate or more severe toxicities develop and to seek further advice from their oncology team (physician, nurse, or pharmacist), if necessary. Patients should be reassured that efficacy will not be compromised if their treatment is interrupted or the dose modified. Follow-up procedures, such as telephone calls to remind patients of the procedure if they experience grade 2 or more severe adverse events, have been effective in improving the safety profile of capecitabine. Current trials are exploring dose reduction at the first occurrence of grade 2 toxicities with the aim of further improving the safety profile of capecitabine.

Several approaches are used for the management of hand-foot syndrome, one of the more common side effects of capecitabine that is typical of prolonged exposure to cytotoxics either through protracted administration schedules (e.g., 5-FU or vinorelbine) [42, 43] or through using preparations with a long half-life (e.g., liposomal doxorubicin) [20]. In patients receiving capecitabine, the first and most important action in managing hand-foot syndrome is to interrupt treatment if the palms or soles become painful. Prophylactic or symptomatic treatment with emollients (e.g., ‘bag balm’) and high-dose vitamin B<sub>6</sub> (>100 mg/day) may provide some relief, although there is currently no clinical evidence from comparative studies regarding the efficacy of vitamin B<sub>6</sub>.

**CONCLUSION**

Four large studies have confirmed that capecitabine is a valuable, active, oral chemotherapy for the treatment of metastatic breast cancer. Single-agent capecitabine resulted in median survival durations of approximately 1 year and a disease control rate of approximately 60% in patients who have been previously treated with an anthracycline and a taxane. No other agent has consistently demonstrated high efficacy in a large population of patients (n = 500) with metastatic breast cancer following taxane treatment (Fig. 5). Furthermore, capecitabine has a favorable safety profile, with a particularly low incidence of myelosuppression and alopecia. Based on data described in this paper, capecitabine has gained regulatory approval for the treatment of patients with taxane-pretreated (paclitaxel-pretreated in the U.S.) metastatic breast cancer in more than 50 countries worldwide and is the only approved therapy in this setting. Oral capecitabine also fulfills patients’ preference for convenient, effective therapy. It is now regarded by many oncologists as the reference treatment for patients with taxane-pretreated metastatic breast cancer.

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