The Role of Capecitabine in First-Line Treatment for Patients with Metastatic Breast Cancer

KAREN GELMON,a ARLENE CHAN,b NADIA HARBECKc

aBritish Columbia Cancer Agency, Vancouver, Canada; bMount Hospital, Perth, Australia; cDepartment of Obstetrics and Gynecology, Technical University of Munich, Munich, Germany

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Abstract
Capecitabine is an important drug in the therapeutic armamentarium for metastatic breast cancer. A comprehensive worldwide clinical trial program involving >10,000 patients with locally advanced and metastatic breast cancer has provided evidence for the current treatment strategies. On the basis of data demonstrating consistent activity across several trials in patients with heavily pretreated breast cancer, capecitabine was approved in the U.S. in 1998 for the treatment of patients with metastatic disease resistant to paclitaxel and anthracycline-containing therapy, with later European Union approval for single-agent capecitabine in the metastatic setting. Capecitabine plus docetaxel (XT) was approved by the U.S. Food and Drug Administration for the treatment of metastatic breast cancer in 2001 on the basis of the large phase III trial comparing XT with docetaxel alone, which showed a survival advantage for combination therapy compared with single-agent therapy. This was shortly followed by European approval for the combination in metastatic breast cancer. The clinical utility of capecitabine in the management of breast cancer is supported by its convenient oral dosing schedule and favorable safety profile, as well as its excellent clinical activity in primary and metastatic breast cancer. Recently, clinical trials have studied single-agent capecitabine as first-line treatment and evaluated other capecitabine-containing combinations with cytotoxic and novel targeted agents. The Oncologist 2006;11(suppl 1):42–51

Introduction
The heterogeneity of metastatic breast cancer (MBC) underlies the need to select therapies taking into account tumor and patient characteristics, and it is clear that both combination chemotherapy and sequential strategies have a role in the metastatic setting. In patients with hormone receptor-positive breast cancer, endocrine therapy will be used at some stage during the course of the disease, if patient and disease characteristics allow. Chemotherapy is indicated in the palliative setting when the disease is endocrine unresponsive or hormone-receptor negative, or when disease characteristics make a rapid response necessary. In the premenopausal setting, treatment may include tamoxifen, alone or together with ovarian suppression, and in the postmenopausal setting, an aromatase inhibitor (such as anastrozole, letrozole, or exemestane) or fulvestrant. Trastuzumab (Herceptin®; F. Hoffmann-La Roche, Basel, Switzerland) has been studied as a single agent and in combination with several chemotherapies and has shown a survival benefit in patients with human epidermal growth factor receptor 2 (HER-2)-positive disease [1–4], making it an optimal standard of care for HER-2-positive breast cancer. Initial data on combined trastuzumab and anastrozole in advanced breast cancer appear promising [5].

Correspondence: Nadia Harbeck, M.D., Ph.D., Department of Obstetrics and Gynecology, Technical University of Munich, Ismaninger Strasse 22, 81675 Munich, Germany. Telephone: 49-89-4140-4596; Fax: 49-89-4140-4846; e-mail: nadia.harbeck@lrz.tum.de Received June 13, 2006; accepted for publication June 21, 2006. ©AlphaMed Press 1083-7159/2006/$20.00/0

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Patients with metastatic disease that is hormone-receptor negative and HER-2 negative should be offered chemotherapy alone. The most commonly used cytotoxic agents are anthracyclines, taxanes, capecitabine (Xeloda®; F. Hoffmann-La Roche), vinorelbine, liposomal doxorubicin, and bevacizumab. These agents can be used as monotherapy or in double (or rarely in triple) combinations depending on patient and disease characteristics. Triple-drug therapy is seldom used, as improved patient outcomes have not been shown, and it is frequently associated with increased toxicity. In addition to trastuzumab, a number of novel agents, including targeted agents such as bevacizumab and laptatinib, as well as new cytotoxics, such as epothilones and albumin-bound paclitaxel, are being investigated for the treatment of MBC and will provide more therapeutic strategies.

Determinants of survival for patients with metastatic disease include: hormone-receptor status, disease-free interval (disease aggressiveness and responsiveness to prior therapy), predominant site of metastases, number of metastatic sites, age, performance status, and comorbidities. Individual patient needs and characteristics (including personal circumstances and preferences) must be considered when deciding which treatment should be administered. An aggressive combination regimen such as capecitabine plus docetaxel (XT) may offer highly effective disease control and an established survival benefit compared with docetaxel alone [6] and may be particularly suited to patients with rapidly progressing disease and/or visceral metastases. Patients with more indolent disease, older patients, or patients wishing to avoid alopecia would be more suited to a less aggressive approach with single-agent chemotherapy such as capecitabine. Either combination or sequential therapy would be suitable for all other patients. The physician needs to discuss with the patient the goals of the therapy proposed and the relative value of differing efficacy and safety end points. In this way, an optimal individualized management strategy can be developed for each patient.

Several factors make capecitabine an ideal agent for the treatment of MBC. The cytotoxic agent 5-fluorouracil (5-FU) is generated from capecitabine by a three-step enzymatic conversion. In the final conversion step, thymidine phosphorylase, which is highly active in tumor tissue, converts 5´-DFUR to 5-FU, culminating in the release of 5-FU directly into tumor tissue. 5-FU, therefore, is delivered preferentially to the tumor by this unique mechanism of action [7]. In addition to its localized tumor activation, capecitabine has demonstrated synergistic activity in vivo with a wide range of other cytotoxic and biologic agents, including taxanes, anthracyclines, mitomycin C, oxaliplatin, bevacizumab, cyclophosphamide, interferon-γ, radiotherapy, gemcitabine, vinorelbine, epidermal growth factor receptor inhibitors, and trastuzumab [8–17]. Finally, the favorable toxicity profile of capecitabine contributes to its prominent role in the treatment of MBC.

**Single-Agent Chemotherapy in the First-Line Treatment of MBC**

The efficacy of first-line capecitabine compares favorably with that of paclitaxel (Table 1) [18]. Based on the intent-to-treat analysis of a trial comparing capecitabine with paclitaxel, an objective response rate of 36% was observed in patients receiving intermittent capecitabine, with three patients (14%) showing a complete response. In patients randomized to paclitaxel, the response rate was 26%, with no complete responses. The median times to disease progression (TTP) were 3.0 and 3.1 months in the capecitabine and paclitaxel groups, respectively. Overall survival was similar in the two treatment groups, with median survival times of 7.6 months with capecitabine and 9.4 months with paclitaxel ($ p = $ nonsignificant).

Similarly, the efficacy of first-line capecitabine compares favorably with that of combination chemotherapy. O’Shaughnessy et al. [19] randomized women to receive either capecitabine or cyclophosphamide, methotrexate, and fluorouracil (CMF) at doses of 600, 40, and 600 mg/m², respectively, once every 3 weeks and reported an objective response rate of 30% in patients receiving capecitabine, with 5% of patients showing a complete response (Table 1). In patients randomized to CMF, the response rate was 16%, with no complete responses. Capecitabine compared favorably with CMF in terms of both TTP and overall survival.

First-line capecitabine monotherapy is also highly effective in patients who are older than 65 years, and a side effect-driven dose reduction from 1,250 mg/m² twice daily to 1,000 mg/m² twice daily did not seem to compromise efficacy (Table 1) [20]. Capecitabine at a dose of 1,250 mg/m² twice daily on days 1–14, every 21 days, was given to the first 30 patients, with a reduction to 1,000 mg/m² in the following 43 patients as a result of adverse events. In these patients, the response (Table 1). In patients randomized to CMF, the response rate was 16%, with no complete responses. Capecitabine compared favorably with CMF in terms of both TTP and overall survival.

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times were 10.0 months with capecitabine 1,250 mg/m² and 16.0 months with capecitabine 1,000 mg/m²; this latter group achieved a higher dose intensity because of a lower incidence of toxicity with the lower dose.

A randomized phase III study has compared the efficacy of sequential single-agent capecitabine followed by a taxane with XT or capecitabine–paclitaxel (XP) combination regimens [21]. In that trial, first-line single-agent capecitabine achieved an impressive response rate of 58% (Table 1). The progression-free and overall survival times in the sequential treatment arm include only those patients who received no further treatment or a taxane after capecitabine.

Cross-trial comparison must be approached with caution but does suggest that first-line capecitabine has similar efficacy to that of anthracyclines and taxanes in the treatment of MBC. Studies report a response rate of 30%–58% for first-line capecitabine [19–21] and a response rate of 36% for combined first-/second-line capecitabine [18]. This is comparable with other agents, including first-line anthracyclines, with response rates of 36%–41% [22, 23]; docetaxel, with response rates of 23%–42% in anthracycline-pretreated MBC [24–28]; and paclitaxel, with response rates of 14%–34% in anthracycline-pretreated MBC [22, 23, 25, 29–31]. Currently, several phase II and III trials are further evaluating capecitabine as a first-line agent. In Germany, the phase II MONo effICAcy of capecitabine (MONICA) trial (principal investigator, M. Kaufmann, Frankfurt) is evaluating the efficacy of capecitabine monotherapy (1,000 mg/m² twice daily) and the PEgylated LIposomal doxorubicin versus CApecitabiNe as first-line chemotherapy for metastatic breast cancer (PELICAN) trial (principal investigator, Nadia Harbeck, Munich) is comparing capecitabine (1,250 mg/m² twice daily) with pegylated liposomal doxorubicin (50 mg/m² every 28 days).

### Evidence for Capecitabine Monotherapy in Patients Pretreated with Anthracyclines and Taxanes

A challenge facing oncologists is the increasing number of patients who have been exposed to active agents, such as paclitaxel and docetaxel, earlier in the disease course, either in the adjuvant setting or as first-line treatment for MBC. Some of these patients are refractory to these agents, while others have experienced significant toxicity with these drugs. In five phase II trials, capecitabine demonstrated consistently high activity in taxane-pretreated disease, with disease control in approximately two thirds of patients (57%–63%) and a median survival time of approximately 1 year [32–36]. This led to a licensed indication in this setting in >80 countries worldwide. The median TTP (3.0–4.9 months) and overall survival time (10.4–15.2 months) seen in these five studies are consistent with those achieved with single-agent capecitabine used earlier in the disease course.

In contrast, in taxane-pretreated patients, vinorelbine achieves only modest efficacy with a wide range of response rates reported, from as little as 0% to 35% [37, 38]. A phase III study of vinorelbine versus liposomal doxorubicin in this setting demonstrated a response rate of 12% for the vinorelbine arm versus 10% with liposomal doxorubicin [39]. Gemcitabine monotherapy has low but variable efficacy in taxane-pretreated patients, ranging from 0% to 29% [40, 41]. In anthracycline- and taxane-pretreated disease, standard capecitabine monotherapy results in a median overall survival time of approximately 1 year [32–36]. This compares very favorably with the overall survival times reported in trials of single-agent vinorelbine, docetaxel, or gemcitabine evaluated in this setting in similar patient populations [40, 42–45].

### Table 1. Efficacy of single-agent capecitabine in front-line metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen (capecitabine dose twice daily, mg/m²)</th>
<th>Response rate (%)</th>
<th>Complete response (%)</th>
<th>Median time to progression (mos)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talbot et al. [18]</td>
<td>Capecitabine 1,250 (n = 22)</td>
<td>36</td>
<td>14</td>
<td>3.0</td>
<td>7.6</td>
</tr>
<tr>
<td>O’Shaughnessy et al. [19]</td>
<td>Capecitabine 1,250 (n = 61)</td>
<td>30</td>
<td>5</td>
<td>4.1</td>
<td>19.6</td>
</tr>
<tr>
<td>Bajetta et al. [20]</td>
<td>Capecitabine 1,250 (n = 30)</td>
<td>37</td>
<td>3</td>
<td>3.9</td>
<td>10.0</td>
</tr>
<tr>
<td>Bajetta et al. [20]</td>
<td>Capecitabine 1,000 (n = 43)</td>
<td>35</td>
<td>2</td>
<td>4.1</td>
<td>16.0</td>
</tr>
<tr>
<td>Reynoso et al. [21]</td>
<td>Capecitabine 1,250 (n = 62)</td>
<td>58</td>
<td>18</td>
<td>8.6 d</td>
<td>31.0 d</td>
</tr>
</tbody>
</table>

a Randomized trial versus paclitaxel.
b Randomized trial versus cyclophosphamide, methotrexate, and fluorouracil.
c Randomized trial versus capecitabine plus docetaxel or capecitabine plus paclitaxel.
d Includes patients receiving a taxane following single-agent capecitabine.
Capecitabine is well tolerated, with a favorable safety profile (Fig. 1) [46]. Among the >700 taxane-pretreated patients treated in the five clinical trials submitted to the regulatory authorities for capecitabine’s approval in MBC, there were no treatment-related deaths. Complete hair loss and myelosuppression were rare [32–36]. The most common adverse event was hand–foot syndrome (or palmar–plantar erythrodysesthesia), a cutaneous side effect that may be debilitating but is always reversible. Grade 2 hand–foot syndrome can be treated effectively with dose interruption, with resumption at a lower dose if necessary after recovery. Patients should be advised to recognize hand–foot syndrome and to contact their health care professional if this side effect occurs. Emollients, with or without oral vitamin B₆ preparations, are common preventive/supportive measures. Gastrointestinal adverse events (diarrhea and stomatitis) were the next most common side effects seen but were largely mild to moderate in intensity and could be effectively managed with medical intervention (e.g., loperamide and rehydration for diarrhea, mouthwash and fluconazole for stomatitis). It is very important that patients are educated to recognize grade 2 adverse events and are instructed to stop treatment and seek medical advice if they occur. Together with appropriate dose modification, the incidence of grade 3 or 4 adverse events can be minimized without compromising efficacy.

Quality of life (QoL) was evaluated in women with anthracycline- and/or taxane-pretreated MBC receiving single-agent capecitabine using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30, v3.0 and the breast cancer-specific module BR-23 [47]. Of 1,125 patients, at least 70% had stable or improved QoL for most scales during capecitabine treatment, including functional and symptomatic QoL (Fig. 2). Patients receiving capecitabine also had a significant improvement (p < .0001 unless stated) in the following: global health status, role and emotional functioning, social functioning (p = .0004), fatigue, nausea/vomiting, pain, insomnia, appetite loss, constipation, diarrhea, financial problems, body image, future perspective, systemic therapy side effects, breast symptoms, arm symptoms (p = .0085), and hair loss. These findings highlight the importance of considering QoL alongside well-established measures of clinical evaluation in patients with metastatic disease.

Dosing Options with Single-Agent Capecitabine

In one of the pivotal trials of capecitabine monotherapy for pretreated MBC, half of the patients had their original capecitabine dose (1,250 mg/m² twice daily) reduced to 1,000 mg/m² twice daily or less [33]. A subset analysis of these patients showed that dose reduction did not have an adverse effect on efficacy as assessed by TTP (hazard ratio [HR], 0.918). Therefore, patients can be reassured that if capecitabine dose reduction is required because of toxicity, the efficacy of their treatment will not be affected.

The 1,000 mg/m² twice-daily dose of capecitabine is a well-tolerated initial dose for older or less fit patients. The study by Bajetta et al. [20] assessed the efficacy and safety of two different capecitabine regimens in 73 elderly patients. There was a low incidence of grade 3 or 4 adverse events in both study groups. The 1,000 mg/m² twice-daily dose of capecitabine was particularly well tolerated, with lower incidences of grade 3 or 4 diarrhea and fewer dose reductions than with the 1,250 mg/m² twice-daily dose of capecitabine.

Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/minute). In patients with moderate renal impairment at baseline (creatinine clearance of 30–50 ml/minute), a lower capecitabine dose (950 mg/m²) is recommended. In patients with mild renal impairment (creatinine clearance of 50–75 ml/minute), the 750 mg/m² dose is recommended.
renal impairment at baseline, capecitabine should be given at the standard starting dose with careful monitoring. As creatinine clearance declines with age, elderly patients will also typically receive the lower starting dose of capecitabine.

**Expanding Treatment Options with Capecitabine–Taxane Combinations**

The coadministration of capecitabine and docetaxel (XT) results in synergistic antitumor activity in the MX-1 breast cancer xenograft model compared with either agent alone [48]. However, toxicity was not increased, as assessed by measurement of body weight.

An international, randomized, phase III trial compared XT with docetaxel monotherapy in patients with anthracycline-pretreated MBC [6]. The tumor response rate was significantly higher with XT than with docetaxel (42% vs. 30%; \( p = .006 \)), while the rates of disease stabilization were similar (38% vs. 44%, respectively). TTP was significantly superior with the combination (log-rank \( p = .0001 \); HR, 0.652; 95% confidence interval [CI], 0.545–0.780). The primary objective of the study, demonstrating superior TTP with XT in patients with MBC compared with docetaxel monotherapy, was clearly met with a median TTP of 6.1 months (95% CI, 5.4–6.5) with XT and 4.2 months (95% CI, 3.4–4.5) with docetaxel. Most importantly, overall survival was significantly superior in patients receiving XT compared with docetaxel \( (p = .0126; \text{HR}, 0.775; 95\% \text{ CI}, 0.634–0.947) \). This translates into patients receiving XT being 23% less likely to die during the study period than those receiving docetaxel. Median survival times were 14.5 months (95% CI, 12.3–16.3) with XT and 11.5 months (95% CI, 9.8–12.7) with docetaxel.

This multicenter, phase III study was the first clinical trial in which a cytotoxic combination regimen provided a significant survival advantage over monotherapy in this patient population and led to the approval of XT for patients with MBC failing anthracycline therapy. The survival benefit with XT was seen early in the course of treatment, with the curves clearly separating at an early stage. Because patients in the combination arm received a lower dose of docetaxel than those receiving docetaxel monotherapy, the survival benefit with XT can be attributed to the addition of capecitabine. Subgroup analysis of the poor-prognosis patients who had relapsed within 2 years of receiving adjuvant anthracyclines found that they also received a clinical benefit from the XT combination [46]. In this group of patients, the median overall survival time was 14.4 months with XT \((n = 67)\), versus 12.0 months with docetaxel \((n = 66)\).

An open-label, single-center, randomized trial of XT versus sequential single-agent docetaxel followed by single-agent capecitabine after progression in first-line MBC was recently presented [49]. Patients were randomized to receive at least 6 weeks of first-line treatment with XT (approved dose; \( n = 50 \)) or sequential docetaxel (100 mg/m²) followed by capecitabine after progression \((n = 50)\). Combination XT was significantly more active than sequential docetaxel followed by capecitabine in first-line MBC even though 74% of patients from the sequential group crossed over to capecitabine monotherapy on disease progression. XT versus docetaxel followed by capecitabine achieved statistically superior efficacy in all end points with extremely favorable HRs translating into a 47% lower risk for both progression and death (Fig. 3). Previously, a large, multicenter, phase III trial had demonstrated that a combination regimen (doxorubicin plus paclitaxel) showed better disease control but did not improve either survival or QoL compared with sequential single-agent therapy [22]. In contrast, in a smaller trial, Beslija et al. [49] did demonstrate a survival benefit for a combination regimen (XT) compared with the sequential administration of the same agents.

The tolerability of XT has hindered its uptake by some physicians and does limit its applicability for all patients. However, with appropriate dose modifications, XT demonstrates a more manageable safety profile. In the pivotal phase III trial [6], grade 4 adverse events were less frequent in the XT arm than in the monotherapy arm (25% vs. 31%, respectively), largely as a result of the higher incidence of neutropenic fever with docetaxel monotherapy. The Beslija et al. [49] trial confirmed that gastrointestinal toxicity and hand–foot syndrome were more common with XT but again that docetaxel monotherapy was associated with greater hematologic toxicity.
A reduction in grade 3 or 4 adverse events is seen if the doses of capecitabine and docetaxel are both reduced [46]. The impact of dose reduction on the tolerability and efficacy of XT was analyzed retrospectively. By reducing capecitabine and docetaxel to 75% of the starting dose (from 1,250 mg/m² to 1,000 mg/m² and 75 mg/m² to 60 mg/m², respectively), the proportion of treatment cycles with grade 3 or 4 treatment-related adverse events was approximately halved [46]. The Kaplan-Meier curves for TTP and overall survival in patients with and without XT dose reductions (cycle 2 onwards) were similar, indicating that capecitabine and docetaxel dose reduction did not compromise efficacy in terms of these end points. Lower initial doses of capecitabine and docetaxel are being prospectively evaluated in the adjuvant setting. Preliminary reports indicate that side effects are less with the lower doses, but efficacy of XT is not compromised [50, 51].

In several studies, capecitabine plus 3-weekly or weekly paclitaxel (XP) has also demonstrated high activity in first-line MBC (Table 2), including response rates in the range of 40%–73% and an overall survival time of up to almost 30 months [52–56]. This combination has a favorable safety profile with a low incidence of grade 3 or 4 adverse events. The most common treatment-related grade 3 or 4 adverse events with the 3-weekly schedule were neutropenia, alopecia, and hand–foot syndrome. The only grade 4 adverse events were neutropenia and fatigue. The most common grade 3 or 4 adverse events for the combination of capecitabine plus weekly paclitaxel were hand–foot syndrome, neutropenia, and nail toxicity.

**Table 2**. Capecitabine plus paclitaxel: consistent activity in metastatic breast cancer

<table>
<thead>
<tr>
<th>Location</th>
<th>Study</th>
<th>Paclitaxel regimen</th>
<th>Pretreated</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.U.</td>
<td>Batista et al. [53]</td>
<td>q3w</td>
<td>Anthracycline</td>
<td>72</td>
<td>52</td>
<td>16.5</td>
</tr>
<tr>
<td>U.S.</td>
<td>Gradishar et al. [52]</td>
<td>q3w</td>
<td>94% first-line</td>
<td>47</td>
<td>51</td>
<td>29.9</td>
</tr>
<tr>
<td>U.S.</td>
<td>Blum et al. [56]</td>
<td>q1w</td>
<td>Anthracycline</td>
<td>55</td>
<td>50</td>
<td>NR</td>
</tr>
<tr>
<td>E.U.</td>
<td>Susnjar et al. [54]</td>
<td>q1w</td>
<td>Anthracycline</td>
<td>11</td>
<td>73</td>
<td>NR</td>
</tr>
<tr>
<td>E.U.</td>
<td>Uhlmann et al. [55]</td>
<td>q1w</td>
<td>Anthracycline</td>
<td>15</td>
<td>40</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: E.U., European Union; NR, not reported; q1w, every week; q3w, every 3 weeks; U.S., United States.

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The efficacy of first-line, single-agent capecitabine compares well with that of the combination regimens. Although both XT and XP tended to produce a higher response rate (almost 80%) than single-agent therapy, there was no significant survival difference between single-agent capecitabine and either combination regimen at this analysis, with the median progression-free and overall survival times similar in the three groups (Table 3). These data differ from those shown in the Beslija et al. [49] trial, and a possible explanation may be the order of sequencing of the single agents. Of note, fewer patients in the sequential arm went on to receive a taxane following progression on capecitabine; this was primarily because, by the time they progressed, patients were no longer considered fit enough for taxane treatment. This begs the question as to whether taxanes following capecitabine are necessary because overall survival was similar with capecitabine monotherapy.

The MOSG study also evaluated the impact on cost for sequential versus combination therapy [21]. The total average cost per patient was calculated as global toxicity cost (toxicity management plus days of treatment delay for this cause) plus treatment cost (drugs and administration). Sequential treatment was the least expensive option, followed by XP (29% more than the single-agent sequence) and then XT (131% more than the single-agent sequence). In terms of quality-adjusted life years (QALY) gained and average cost of each treatment per QALY, XP was more expensive and less effective than sequential therapy, and XT was more expensive but also more effective than sequential therapy. This shows that sequential capecitabine and taxane therapy is a dominant (less expensive and as effective) treatment strategy compared with XP and is more cost-effective than XT.

**FURTHER OPTIONS WITH CAPECITABINE-CONTAINING COMBINATIONS**

Capecitabine plus i.v. vinorelbine (XN) has shown consistently high activity in anthracycline- and taxane-pretreated patients with MBC. In five phase II studies, XN achieved response rates of 40%–68% [57–61]. This combination is...
well tolerated, with the most common treatment-related adverse event being myelosuppression. Completely oral combinations of both drugs are under development [62].

Capecitabine combined with bevacizumab is active and well tolerated in heavily pretreated MBC [36]. Efficacy results showed a 19% response rate without bevacizumab and a 30% response rate with bevacizumab, and the median progression-free survival times were 4.2 months without bevacizumab and 4.9 months with bevacizumab. The median overall survival times were 14.5 months without bevacizumab and 15.1 months with bevacizumab. The TTP and survival differences were not statistically significant. The only grade 3 or 4 adverse event that was more frequent in patients receiving bevacizumab was hypertension (17.9% vs. 0.5%). A large ongoing trial program is investigating this combination earlier in the disease course.

Capecitabine-based therapy has also been evaluated in HER-2-positive MBC, and the first phase III trial will report in 2006. Capecitabine plus trastuzumab has shown high first-line activity [3] and is also highly active in patients with pretreated disease [63, 64]. In the first-line setting, the overall response rate was 73%, including a 15% complete response rate. An additional eight patients (20%) had stable disease, leading to a clinical benefit in 93% of patients [3]. The only grade 3 or 4 adverse events were hand–foot syndrome in four patients and leukopenia in one patient, but both resolved with dose interruption or reduction. There were no episodes of grade 4 adverse events, grade 3 diarrhea or vomiting, or cardiac dysfunction. In patients with pretreated disease, Yamamoto et al. [64] demonstrated a partial response in 41% of patients and a further nine patients had stable disease. The median TTP was 5.2 months, and median overall survival time was 16.1 months. There were no grade 3 or 4 adverse events. In a second study of capecitabine and trastuzumab in patients with pretreated disease, the overall response rate was 52%, including four complete responses (17%) [63]. The median TTP was 6.4 months, and median overall survival time was 20.7 months. Grade 3 or 4 anemia and leukopenia were seen in 8% and 4% of patients, respectively.

Grades 3 or 4 nonhematologic toxicities included general aches, hand–foot syndrome, vomiting, and nausea.

Currently, an open-label, randomized, phase II study is evaluating a triple combination of capecitabine with docetaxel and trastuzumab (HTX) versus docetaxel plus trastuzumab (HT) alone. Thus far, safety data are available from 110 patients [4]. Grade 3 or 4 neutropenia occurred in 52% of patients in the HTX arm and in 76% of patients in the HT arm. The overall incidence of complicated neutropenia (febrile neutropenia, neutropenic infection, or neutropenic sepsis) was 26%. The overall incidence of symptomatic congestive heart failure was 2% (one patient in each treatment arm), which lies within the expected range for patients receiving trastuzumab plus chemotherapy (3%–4%). The HTX regimen has favorable safety in terms of grade 3 or 4 neutropenia, probably because of the lower dose of docetaxel used.

A recent study has reported data on the combination of capecitabine plus oral vinorelbine with or without trastuzumab [65]. The preliminary results confirm optimal disease control rates (response rate plus stable disease) of 93% in HER-2-negative disease (without trastuzumab) and 92% in HER-2-positive disease (with trastuzumab). The all-oral capecitabine–vinorelbine combination was well tolerated, and the addition of trastuzumab in HER-2-positive patients did not alter the favorable safety profile.

### Table 3. First-line capecitabine sequence compares favorably with combinations [21]

<table>
<thead>
<tr>
<th></th>
<th>XT (n = 71)</th>
<th>XP (n = 73)</th>
<th>X followed by a taxane (n = 62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (%)</td>
<td>76</td>
<td>73</td>
<td>58</td>
<td>.06</td>
</tr>
<tr>
<td>Complete response</td>
<td>21</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Median PFS (mos)</td>
<td>10.1</td>
<td>9.2</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>12-month survival (%)</td>
<td>82</td>
<td>76</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Median survival (mos)</td>
<td>34</td>
<td>29</td>
<td>31</td>
<td>.77</td>
</tr>
</tbody>
</table>

**Abbreviations:** NS, not significant; PFS, progression-free survival; X, capecitabine; XP, capecitabine plus paclitaxel; XT, capecitabine plus docetaxel.

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**Figure 4.** North Central Cancer Treatment Group 0432: phase II trial of first-line capecitabine–docetaxel–bevacizumab combination therapy (n = 46).
A phase II study of capecitabine in combination with docetaxel and bevacizumab (the North Central Cancer Treatment Group 0432 trial) has just completed accrual (Fig. 4), and efficacy data, including time-related parameters, will be reported at the San Antonio Breast Cancer Symposium in 2006.

CONCLUSIONS
Single-agent, first-line capecitabine is a highly effective and well-tolerated option that may be appropriate for several groups of patients, including patients with slowly progressive disease and those who prefer oral treatment, wish to avoid hair loss, are older, or are less fit. In addition, patients with exposure to taxanes in the adjuvant setting may benefit from first-line capecitabine. Furthermore, capecitabine allows patients to benefit from a long-term treatment that can lead to prolonged survival without the risk for cumulative toxicity. This will be particularly important with the advent of novel targeted agents in long-term treatment, because capecitabine is the only cytotoxic combination partner with no cumulative toxicity. Capecitabine compares well with the most active agents in breast cancer and should be considered to be an essential component of combination treatment for MBC. It is highly effective in first-line treatment and, when used in combination therapy, has demonstrated overall survival benefits beyond docetaxel alone in two randomized studies. As an oral agent, capecitabine is a flexible combination partner that has a favorable safety profile with minimal myelosuppression and alopecia. Capecitabine allows treatment to be individually tailored to meet each patient’s needs with dosing flexibility, which allows better management of side effects. As such, capecitabine can also be an ideal maintenance treatment.

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