Capecitabine: Expanding Options for the Treatment of Patients with Early or Locally Advanced Breast Cancer

ANDREW WARDLEY

Christie Hospital and South Manchester University Hospital, Manchester, United Kingdom

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Abstract
Capecitabine has proven efficacy in metastatic breast cancer, extending survival in combination with docetaxel and offering a favorable safety profile, including minimal myelosuppression and alopecia, as a single agent. It is therefore logical that capecitabine could build on the improved outcomes achieved with taxanes in early breast cancer. In the neoadjuvant setting, a phase III trial of capecitabine and docetaxel (XT) versus doxorubicin and cyclophosphamide (AC) showed that XT was more effective than AC in terms of clinical response rate and pathologic complete response rate, with a manageable safety profile. Other studies, including a phase III trial of capecitabine, epirubicin, and docetaxel, a phase III trial of capecitabine and vinorelbine, and several phase II studies of different regimens with capecitabine, have confirmed the high activity of neoadjuvant capecitabine, with acceptable safety. In the adjuvant setting, a Finnish phase III study (FinXX) of sequential XT followed by cyclophosphamide, epirubicin, and capecitabine versus docetaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide has shown favorable safety with lower doses of both capecitabine and docetaxel in the XT combination. Efficacy results from that trial are eagerly awaited. A large, ongoing trial program is continuing to explore the potential for capecitabine in the treatment of early breast cancer, looking at capecitabine–taxane combinations, capecitabine maintenance therapy, capecitabine for elderly patients, and sequential versus combination therapy, involving >20,000 patients. The Oncologist 2006;11(suppl 1):20–26

Introduction
The goals of chemotherapy in the adjuvant setting are to decrease the risk of disease recurrence and to prolong survival [1, 2]. In the neoadjuvant setting, the goals of chemotherapy are to downstage tumors and to increase the rate of breast-conserving surgery [3, 4]. Neoadjuvant chemotherapy provides early introduction of systemic chemotherapy in a disease with a high recurrence rate and allows in vivo assessment of sensitivity. It provides an excellent opportunity to obtain biological samples for research. Of all breast cancer patients eligible for adjuvant treatment, approximately half receive chemotherapy. The other half receive hormonal therapy (for patients with hormone receptor-positive tumors) or surgery and/or radiotherapy only. Most patients receive adjuvant as opposed to neoadjuvant chemotherapy (85%); however, numerous studies have compared neoadjuvant with adjuvant chemotherapy and have shown similar disease-free and overall survival rates [5]. Neoadjuvant chemotherapy also has the added advantage of improving surgical options.

Data from multiple clinical trials have indicated that pathological complete response (pCR) (i.e., no residual cancer in the breast or lymph nodes) after neoadjuvant chemotherapy is associated with an excellent long-term prognosis [6]. The use of pCR rates in neoadjuvant chemotherapy trials as a study end point has several implications [7]. First, it serves as an ultimate goal for response: complete disappearance of the tumor is a worthy end point for...
systemic chemotherapy, and pCR is currently the best surrogate for elimination of microscopic metastatic disease, as evidenced by long-term survival data. (Although this conclusion is not wholly supported by the pivotal National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial [8], it does not go against this idea.) Second, a greater pCR rate for a novel therapy would suggest that such an agent could result in ultimate clinical benefits, and many neoadjuvant chemotherapy trials have thus been designed with the pCR rate as the primary end point.

In many countries the standard of chemotherapy care for early breast cancer (EBC) is an anthracycline-containing combination with concurrent or sequential taxanes. Block sequential regimens are increasingly used with three to four cycles of an anthracycline followed by a taxane or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). In the neoadjuvant setting, docetaxel already has proven activity. The NSABP B-27 trial showed that the addition of four cycles of preoperative docetaxel after four cycles of preoperative doxorubicin and cyclophosphamide (AC) for operable breast cancer resulted in significantly higher clinical and pathologic response rates (the pCR was double, from 13% to 26%) [8].

In a separate adjuvant study, the addition of docetaxel to AC (TAC) was shown to result in significantly longer disease-free and overall survival times compared with 5-fluorouracil plus AC (p < .001), making TAC one of the most active adjuvant treatments in patients with EBC [9]. Capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland) has considerable promise for use at an earlier point in breast cancer treatment to improve disease-free and overall survival. In combination with docetaxel (Taxotere®; sanofi-aventis, Paris), capecitabine extends survival in patients with metastatic breast cancer (MBC) [10, 11] and is one of the three most active chemotherapy treatments (the others being anthracyclines and taxanes). It is therefore rational that the combination of capecitabine plus docetaxel (XT), which extends survival in patients with MBC, should be studied as an active combination in the neoadjuvant and adjuvant settings.

**Evidence from Phase III Trials of Neoadjuvant Capecitabine-Containing Combinations**

Recently, final results from a randomized, phase III study evaluating XT as neoadjuvant treatment showed that XT has good potential to improve outcomes in EBC [12]. Patients with stage II or III breast cancer were randomized to receive either four cycles of standard AC therapy (doxorubicin, 60 mg/m², and cyclophosphamide, 600 mg/m², both on day 1 of a 21-day cycle) or four cycles of XT (capecitabine, 1,000 mg/m² twice daily on days 1–14, plus docetaxel, 75 mg/m² on day 1 of a 21-day cycle) as neoadjuvant chemotherapy. Following four cycles of preoperative chemotherapy, all patients had surgery followed by a crossover to the other chemotherapy regimen as adjuvant treatment. The primary end point was the pCR rate and the main secondary end point was clinical complete response of neoadjuvant chemotherapy. The treatment arms were well balanced in terms of age, performance status, disease stage, and receptor status.

Overall, 209 patients were enrolled, and 204 patients who had undergone clinical and radiologic evaluation of radiological response and who had completed surgery were included in the final analysis [12]. The analysis showed that XT was more effective than AC. The objective clinical response rates (as assessed by the Response Evaluation Criteria In Solid Tumors [RECIST]) were 84% versus 67%, respectively (p = .0047); only one patient progressed while on XT therapy, compared with eight on AC therapy. A higher pCR rate (a total absence of malignant cells) was achieved in primary tumors (23% vs. 10%, respectively) and lymph nodes (33% vs. 23%, respectively) (Fig. 1), and a greater rate of downsizing was seen in lymph nodes (100% vs. 50%, respectively). Tumor downsizing was similar in the two groups (52% for XT vs. 47% for AC, respectively), and similar rates of breast-conserving surgery were seen for XT and AC (stage II, 84% vs. 70%; stage III, 55% vs. 62%, respectively). This study shows that XT is an active regimen and may represent a valuable alternative to anthracycline-containing combinations, as it may be more amenable to combination with novel agents such as trastuzumab (Herceptin®; F. Hoffmann-La Roche) and bevacizumab (Avastin®, F. Hoffmann-La Roche) with less risk of long-term cumulative adverse events.

In terms of all-grade clinical adverse events, XT caused less nausea (46% vs. 98%), vomiting (19% vs. 85%), and stomatitis (49% vs. 84%), but more diarrhea (41% vs. 15%) and myalgia (77% vs. 28%) than AC. For hematologic adverse events, XT caused less all-grade anemia than AC (66% vs. 70%, respectively) and a similar rate of neutropenia (86% vs. 89%, respectively). XT caused more liver enzyme elevations than AC (alanine aminotransferase, 39% vs. 25%; aspartate aminotransferase, 33% vs. 21%)

In terms of grade 3 or 4 adverse events, XT compared with AC caused less neutropenia (72% vs. 85%, respectively) and vomiting (5% vs. 25%, respectively), but more hand–foot syndrome (22% vs. 0%, respectively) and stomatitis (10% vs. 0%, respectively). It should be noted that, in contrast to anthracycline-containing regimens, the XT combination has not been associated with any long-term cardiac toxicity.

XT is not the only capecitabine-containing combination to have shown promise in a phase III trial. The combination of docetaxel, epirubicin, and capecitabine (TEX) has been

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Figure 1. Capecitabine plus docetaxel (XT) produces a higher pathologic complete response rate than doxorubicin and cyclophosphamide (AC) in primary tumors and lymph nodes [12].

compared with epirubicin plus docetaxel (ET) in a phase III study [13]. Patients with stage III or IV breast cancer were randomized to one of two treatment arms, with cycles of 21 days: the ET regimen (both at 75 mg/m² i.v. on day 1) or the TEX regimen (ET regimen the same as the first arm, plus capecitabine, 1,000 mg/m² twice daily on days 1–14). Patients in both groups were balanced in terms of age, performance status, and disease stage.

A planned interim analysis, after 150 of 285 patients had been treated, showed overall objective response rates of 70% for the TEX group versus 62% for the ET group, with 20% and 8% complete response rates, respectively [13]. The difference in the complete response rate was observed both in stage III patients (18% for TEX vs. 5% for ET) and in stage IV patients (20% for TEX vs. 9% for ET). Discontinuation because of toxicity occurred in six patients in the TEX group and seven patients in the ET group. The main reported grade 3 or 4 toxicities were, in the TEX and ET groups, respectively: diarrhea, 1.5% versus 0.5%; hand–foot syndrome, 1.5% versus 0%; febrile neutropenia, 3.5% versus 3.4%; and neutropenia, 19% versus 14.4%. Three patients in the ET group died of treatment-related toxicity; these doses have been shown to reduce the incidence of side effects associated with XT without compromising the efficacy benefit for patients.

Phase II trials have also provided preliminary promising data for other capecitabine-containing combinations that have achieved high clinical response rates (76%–100%; complete responses in up to 62%) and pCR rates (12%–22%) in the neoadjuvant setting (Table 1) [15–21]. The authors concluded that they had demonstrated equal efficacy for a nontaxane-, nonanthracycline-containing combination, XN, compared with TAC, with a more favorable toxicity profile for XN, with less hematologic toxicity, infections, stomatitis, and nail changes. The tolerability of XN may be even further improved with more flexible dose adjustments in the case of hand–foot syndrome. Patients without a response to TAC could benefit more from a switch to XN rather than continuation with TAC. In view of the relatively low pCR rates achieved with both regimens in breast cancer that is unresponsive to TAC, a different treatment approach to improve patient outcome is clearly needed.

Further Supportive Evidence in the Neoadjuvant Setting

The high activity of XT in the neoadjuvant setting has been confirmed by several phase II studies (Table 1) [15–21]. In the Lebowitz et al. [15] trial, the need for dose reduction in eight of the first 10 patients treated led to a 25% reduction in the doses of both agents being used for subsequent patients: capecitabine reduced from 1,000 mg/m² to 937.5 mg/m², and docetaxel reduced from 75 mg/m² to 60 mg/m². This reduced the incidences of myalgia, diarrhea, and non-neutropenic infection. Of the XT doses studied in phase II trials to date (Table 1), the reduced dose used by Lebowitz et al. [15] is the one recommended for further study, as these doses have been shown to reduce the incidence of side effects associated with XT without compromising the efficacy benefit for patients.

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Recently, a phase II study has also evaluated the efficacy and safety of capecitabine chemoradiation as neoadjuvant therapy in patients with inoperable locally advanced breast cancer refractory to anthracycline therapy [22]. Patients received radiotherapy (2 cGy/day on days 1–5) for 5 weeks plus capecitabine (850 mg/m² twice daily on days 1–14, every 3 weeks). Three fourths of patients were rendered operable by capecitabine chemoradiation: 23 of the 28 evaluable patients (82%) were operable after capecitabine chemoradiation; four patients (14%) did...
not undergo surgery because of disease progression. The median tumor size after capecitabine chemoradiation was 49 cm² (range, 6–126 cm²), a median relative reduction in tumor size of 33%. After surgery, the median residual tumor size was 12 cm² (range, 0–72 cm²) and the median number of positive nodes was two (range, 0–27). Also after surgery, pCR was observed in three patients (11%).

Capecitabine chemoradiation was well tolerated with no grade 3 or 4 adverse events [22]. The most common treatment-related adverse events were mucositis, diarrhea, nausea, and vomiting; all were grade 1 or 2. There were no hematologic/labouratory adverse events. The authors concluded that neoadjuvant capecitabine chemoradiation is effective in patients with anthracycline-refractory locally advanced breast cancer, enabling a high proportion of patients to undergo surgery. It is also extremely well tolerated, with no grade 3 or 4 adverse events reported. These results suggest that a randomized study should be performed comparing capecitabine chemoradiation with radiotherapy alone. The use of capecitabine chemoradiation could also be expanded to the first-line metastatic setting, because it leads to good local tumor control with very few side effects.

**Ongoing Evaluation of Neoadjuvant Capecitabine**

A large ongoing trial program is continuing to investigate the potential of capecitabine-containing combinations in the neoadjuvant setting (Table 2).

### Table 1. Capecitabine-based combinations achieve high response rates in neoadjuvant breast cancer

<table>
<thead>
<tr>
<th>Regimen (mg/m²)a</th>
<th>No. of patients</th>
<th>Clinical response (%)</th>
<th>pCR (%)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine (1,250) on days 1–14; docetaxel (75) on day 1; every 21 days</td>
<td>29</td>
<td>79</td>
<td>17</td>
<td>62</td>
</tr>
<tr>
<td>Capecitabine (900) on days 1–14; docetaxel (36) on days 1 and 8; every 21 days</td>
<td>19</td>
<td>79</td>
<td>11</td>
<td>68</td>
</tr>
<tr>
<td>Capecitabine (937.5–1,000) on days 2–15; docetaxel (60–75) on day 1; every 21 days</td>
<td>29</td>
<td>90</td>
<td>31</td>
<td>59</td>
</tr>
<tr>
<td>Capecitabine (625) on days 5–18; docetaxel (30) on days 1, 8, and 15; carboplatin (AUC = 2) on days 1, 8, and 15; every 28 days</td>
<td>24</td>
<td>93</td>
<td>62</td>
<td>31</td>
</tr>
<tr>
<td>Capecitabine (900) on days 1–14; docetaxel (60) on day 1; cisplatin (50) on day 1; every 21 days</td>
<td>28</td>
<td>100</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Docetaxel (30) on days 1, 8, and 15; doxorubicin (50) on day 1; capecitabine (750) on days 1–14; every 28 days</td>
<td>34</td>
<td>97</td>
<td>31</td>
<td>66</td>
</tr>
<tr>
<td>Epirubicin (60) on day 1; capecitabine (1,000) on days 1–14; cisplatin (60) on day 1; every 21 days</td>
<td>45</td>
<td>76</td>
<td>13</td>
<td>62</td>
</tr>
</tbody>
</table>

*aCapecitabine dose is given twice daily. Abbreviations: AUC, area under the concentration–time curve; pCR, pathologic complete response.*
incidences of grade 3 or 4 neutropenia. However, both capecitabine-based regimens were associated with lower incidences of grade 4 neutropenia than the comparator regimen (Fig. 3) [23]. A second planned safety analysis of 600 patients was recently presented at the American Society of Clinical Oncology Congress 2006, and the efficacy analyses are expected to be available in 2009.

**Ongoing Evaluation of Adjuvant Capecitabine**

Another large, ongoing trial program is evaluating the potential of single-agent capecitabine and capecitabine-containing combinations in various situations in the adjuvant setting (Table 3).

The U.S. Oncology registration trial includes trastuzumab for patients with human epidermal growth factor receptor 2 (HER-2)-positive tumors, and, with >2,000 patients, it will be the definitive trial to show the benefit of XT in the adjuvant setting. Capecitabine has also demonstrated high activity as a front-line single-agent treatment for MBC versus paclitaxel and versus CMF [24, 25]. In addition, efficacy results from five clinical trials show that single-agent capecitabine has consistently high activity in anthracycline- and taxane-pretreated MBC [26–30]. Capecitabine is associated with a favorable safety profile, as it has a low incidence of myelosuppression and minimal alopecia, which, along with the convenience of a home-based oral treatment, makes it ideal for the adjuvant setting. Studies of sequential therapies (the Trial of Accelerated adjuvant ChemoTherapy with capecitabine [TACT]2 and the Grupo Español de Investigación de Cáncer de Mama [GEICAM] trial) are aiming to demonstrate that capecitabine can provide a safer, less toxic, less complicated regimen with equivalent efficacy. The Coalición Iberoamericana de Investigación en Oncología Mamaria (CIBOMA) study evaluating capecitabine as adjuvant maintenance therapy following six cycles of anthracycline-containing therapy is the first trial of this kind to be conducted in the adjuvant setting. The German Adjuvant Intergroup Node-positive (GAIN) study is the only capecitabine trial investigating a dose-dense regimen in the adjuvant setting. Studies in elderly patients (the Cancer and Leukemia Group B [CALGB] 49907 trial and the Ibandronate with or without Capecitabine in Elderly patients [ICE] trial) aim to show the benefits of an oral therapy for this group of patients, particularly in terms of...
Table 3. Evaluation of capecitabine in adjuvant chemotherapy for women with early breast cancer (n > 20,000)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Test arm</th>
<th>Control arm</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>U.S. Oncology</td>
<td>AC→XT</td>
<td>AC→T</td>
</tr>
<tr>
<td>TACT2</td>
<td>E→X</td>
<td>E→CMF</td>
<td>4,400</td>
</tr>
<tr>
<td>GEICAM</td>
<td>ET→X</td>
<td>EC→T</td>
<td>1,302</td>
</tr>
<tr>
<td>CIBOMA</td>
<td>Anthracycline-based→X</td>
<td>Anthracycline-based</td>
<td>3,538</td>
</tr>
<tr>
<td>GAIN</td>
<td>EC→XP</td>
<td>E→P→C</td>
<td>3,130</td>
</tr>
<tr>
<td>CALGB</td>
<td>X</td>
<td>CMF or AC</td>
<td>600</td>
</tr>
<tr>
<td>ICE</td>
<td>Ibandronate + X</td>
<td>Ibandronate</td>
<td>1,394</td>
</tr>
<tr>
<td>MINDACT</td>
<td>XT</td>
<td>AC</td>
<td>5,000</td>
</tr>
<tr>
<td>Neo/adjuvant</td>
<td>MDACC</td>
<td>XT→FEC</td>
<td>930</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; C, cyclophosphamide; CALGB, Cancer and Leukemia Group B; CIBOMA, Coalición Iberoamericana de Investigación en Oncología Mamaria; E, epirubicin; F, 5-fluorouracil; GAIN, German Adjuvant Inter-group Node-positive study; GEICAM, Grupo Español de Investigación de Cáncer de Mama; ICE, Ibandronate with or without capecitabine in elderly patients; M, methotrexate; MDACC, M.D. Anderson Cancer Center; MINDACT, Microarray In Node Negative Disease May Avoid Chemotherapy; P, paclitaxel; T, docetaxel; TACT2, Trial of Accelerated Adjuvant Chemotherapy with capecitabine; X, capecitabine.

of the convenience of home-based administration and the minimal incidence of side effects, which are important for a group of patients who often do not receive active treatment because of comorbidities and advanced age. Finally, the Microarray In Node negative Disease may Avoid Chemotherapy (MINDACT) study is the first study of individualized therapy in which treatment choice will be based on clinical and genomic risk factors.

**Conclusions**

Capecitabine is already showing high efficacy with a manageable safety profile in the neoadjuvant treatment of EBC. Capecitabine has the potential to further improve outcomes in EBC, and several multinational trials are investigating this potential. The high activity of neoadjuvant XT has been confirmed by numerous phase II and III studies, and capecitabine-containing combinations have also demonstrated high activity. A major benefit of capecitabine is that there are no associated long-term toxicities, which is especially important for a group of patients who are otherwise healthy and may have many years still to live. In addition, capecitabine is not contraindicated for use with novel biologic agents that are starting to show great promise, such as trastuzumab and bevacizumab.

A large ongoing trial program aims to translate the survival benefit seen with XT in the metastatic setting into the adjuvant setting. To date, one phase III trial has demonstrated that capecitabine-containing combinations are well tolerated in the adjuvant setting and that the addition of capecitabine to standard sequences in adjuvant breast cancer does not increase toxicity. In addition, single-agent capecitabine can be used in a wide variety of situations, including in elderly patients and as long-term maintenance therapy.

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**Disclosure of Potential Conflicts of Interest**

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