New Directions With Capecitabine Combinations in Advanced Breast Cancer

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Capecitabine (Xeloda) offers a unique mode of action. The drug is currently being combined with other active agents in the treatment of advanced breast cancer. The recent demonstration of improved disease-free and overall survival with the combination of capecitabine (Xeloda) and docetaxel (Taxotere) compared with single-agent docetaxel in anthracycline-pretreated patients indicates the important role of capecitabine in the treatment of advanced breast cancer.

The use of this agent in combination therapy in breast cancer patients, however, has only begun to be explored, as the agent has a unique mode of action and can be combined safely with a variety of agents. Potential for improvement in the therapeutic index of treatment with capecitabine-containing combinations is suggested by (1) activity of other treatments (eg, taxanes, cyclophosphamide [Cytoxan, Neosar], irinotecan [Camptosar], and vinorelbine [Navelbine], as well as radiation therapy) in increasing tumor levels of thymidine phosphorylase, the activating enzyme for capecitabine; (2) early-phase studies showing activity of combinations with a variety of different agents; and (3) preclinical data indicating potential for synergistic effects with a number of combinations.

Combinations With Taxanes

In North America, cyclophosphamide/doxorubicin combinations at full conventional dosages have been the basis of breast adjuvant treatment. Based upon the enhanced response rates of phase III trials in the neoadjuvant setting (National Surgical Adjuvant Breast and Bowel Project trial B-27) and in the adjuvant setting (the Aberdeen trial), cyclophosphamide/doxorubicin followed by docetaxel may offer a new standard approach in the management of early-disease patients. As capecitabine/taxane combinations demonstrate a higher response rate and better survival than docetaxel alone in metastatic disease, the combination is being advanced into treatment of earlier disease. The current US Oncology Adjuvant Trial (XEL242) addresses the question of whether or not the use of capecitabine/docetaxel following classical cyclophosphamide/doxorubicin (Adriamycin) (AC) offers any benefit over single-agent docetaxel following AC. Additional similar studies are in development.

Weekly Taxanes

Weekly taxanes may offer a therapeutic advantage over traditional every-3-week schedules of administration and are being actively studied. Because of the ease of administration of taxanes on a weekly schedule and the possibility of repetitively up-regulating thymidine phosphorylase, additional studies are exploring the feasibility of weekly taxane treatment in combination with capecitabine. Preliminary findings using this approach in 19 anthracycline-pretreated patients with metastatic breast cancer demonstrated activity with acceptable toxicity in an ongoing phase I/II study. The recommended dose was identified as intermittent oral capecitabine at 900 mg/m² twice daily on a 14-day schedule every 3 weeks plus weekly docetaxel at 30 mg/m². There was a low incidence of severe myelosuppression, with only one grade 4 event (neutropenia) being observed; the most common grade 3 toxicity was palmar-plantar erythrodysesthesia (in 3 of 19 patients). Objective tumor response was observed in two patients, with seven patients demonstrating stable disease. Meza et al have reported findings in a phase II study of paclitaxel at 175 mg/m² every 3 weeks, plus capecitabine at 825 mg/m² twice daily on days 1 to 14, as first- or second-line treatment of
metastatic breast cancer.[13] The patients had a median age of 52 years (range: 35-76 years) and a median Karnofsky performance status of 90. Among 47 evaluable patients, 34 patients received this therapy as first-line treatment, and 13 patients as second-line treatment. Of these patients, 13% (five patients with first-line treatment, and one with second-line treatment) achieved a complete response; 30% of patients achieved a partial response; and 38% had stable disease. Because of the small number of patients, there is some variation in the partial responses in patients receiving first- or second-line treatment (Figure 1). Overall, median time to disease progression was 44 weeks.[13] Additional investigations, from which data are not yet available, include study of a capecitabine/docetaxel/trastuzumab (Herceptin) combination and study of sequential epirubicin (Ellence)/docetaxel/capecitabine in the neoadjuvant setting.

**Combinations With Other Agents**

Further strategies for optimizing capecitabine activity include substituting other agents that upregulate thymidine phosphorylase for docetaxel or combining capecitabine with alkylating agents, other standard agents, or biologics (eg, interferon, trastuzumab). Vinorelbine is an attractive agent to combine with capecitabine, as the drug has a good toxicity profile and significant therapeutic activity.[14]

**Capecitabine/Vinorelbine Combination**

Several investigators have reported on the use of the capecitabine/vinorelbine combination. In a phase I study, 40 pretreated patients with advanced or metastatic breast cancer received 21-day cycles of capecitabine at 500 to 1,250 mg/m² twice daily on days 1 to 14 combined with IV vinorelbine at 12.5 to 22.5 mg/m² on days 1 to 3.[15] The maximum tolerated dose of the combination has not yet been defined; preliminary reports indicate that minimal toxicity was observed. Among 33 evaluable patients treated at all dose levels, the objective response rate was 48%.[15] A Swiss phase I/II study enrolled 36 patients, all of whom were 65 years of age or older, and 61% of whom had visceral metastases. As first-line treatment, the group received capecitabine at 800 to 1,250 mg/m² twice daily on days 1 to 14, and vinorelbine at 20 mg/m² IV on days 1 and 8, every 3 weeks.[16] Dose-limiting toxicities were neutropenia, stomatitis, diarrhea, and thrombosis. The maximum tolerated dose of capecitabine was 1,250 mg/m² in patients without bone involvement and 1,000 mg/m² in those with bone involvement. Tumor responses were observed at all dose levels.[16] In a small Korean phase II study, 24 patients with prior anthracycline and taxane exposure, median age of 45 years, and a median of four prior chemotherapy cycles received capecitabine at 1,250 mg/m² twice daily on days 1 to 14, in combination with vinorelbine at 25 mg/m² IV on days 1 and 8, every 3 weeks. The reported overall response rate was 53%.[17]

**Capecitabine/Idarubicin/Cyclophosphamide Oral Combination**

Part of the attractiveness of capecitabine is its ability to be given in oral doses,[18] which allows flexibility in treatment. Capecitabine has been evaluated as part of an oral combination chemotherapy regimen with idarubicin (Idamycin) and cyclophosphamide. Treatment included capecitabine at 1,000 mg/m² twice daily on days 1 to 14, oral idarubicin at 10 mg/m² on days 1, 3, and 5, and oral cyclophosphamide at 100 mg/m² on days 1 to 14, every 3 weeks. A total of 20 patients described as heavily pretreated, with a median age of 52 years, and visceral dominant disease were enrolled in the phase II trial. [19] Objective response was observed in 15% of patients, with 40% having stable disease. Toxicities consisted of grade 3 or 4 diarrhea in 10% of patients, grade 3 vomiting in 10%, and grade 3 or 4 hand-foot syndrome in 15%. One patient had grade 3 neutropenia. The investigators concluded that the combination was active and should be investigated in earlier-stage disease.[19]

**Capecitabine/EGFR Inhibitors Combination**

Another potential approach to enhance the efficacy of capecitabine is to interfere with members of the epithelial growth factor receptor (EGFR) superfamily. HER2/neu, the second member of this superfamily, has been shown to be a therapeutic target.[20] Inhibition of this receptor is associated with additive or synergistic antitumor effects when combined with conventional chemotherapeutic agents for breast cancers over-expressing this receptor.[21] Additional members of this class of receptors can be inhibited by small molecules directed at the receptor's tyrosine kinase activity.[22] We, therefore, have been interested in studying the combination of EGFR inhibitors with capecitabine metabolites in tissue culture as a preclinical model for future human studies.[23] Using human breast cancer cell lines in tissue culture and a median effects model,[24] which allows determination of drug combination effects for cytotoxic synergy, additive effects, or antagonism, we have found
that the combination of capecitabine and an EGFR tyrosine kinase inhibitor (AG-1478)[25] has profound synergy.[23] AG-1478 inhibits all four EGFR receptor subgroups in cells although it was originally believed to be a specific inhibitor of EGFR-1 based upon cell-free assays. The drug exhibits striking synergy with 5'-deoxy-5-fluorouridine (the cytotoxic metabolite of capecitabine) in the MCF7/ADR (Adriamycin [doxorubicin]-resistant) breast cancer cell line (Figure 2). This cell line expresses both the HER2/neu (EGFR-2) receptor and the EGFR-1 receptor.

Similar activity of the combination has been observed in the BT474 breast cancer cell line, which expresses HER2/neu but not EGFR-1.[23] In animal studies using BT474 breast cancer xenografts, the combination of capecitabine and trastuzumab, which inhibits HER2/neu receptors, produced additive if not synergistic effects (Figure 3).[32] Such findings suggest that combinations of capecitabine and EGFR inhibitors may have broad applicability in breast cancer, may be of value in other tumors that overexpress receptors of this class, and should be evaluated in clinical studies. Additional trials currently are assessing combinations of capecitabine with cyclophosphamide/doxorubicin, cyclophosphamide/epirubicin, docetaxel/carboplatin (Paraplatin), and interferon-alfa (Roferon, Intron) in advanced breast cancer patients. No data are yet available for these combinations.

**A Potential Capecitabine/Irinotecan Combination**

Irinotecan recently has been shown to have activity in metastatic breast cancer refractory to either an anthracycline or a taxane.[27] In a randomized phase II study, 102 patients with prior anthracycline or taxane exposure and a maximum of two prior chemotherapy courses in the metastatic setting received irinotecan at 100 mg/m² weekly for 4 weeks, or at 240 mg/m² every 3 weeks, in 6-week cycles.[27] Preliminary data from this trial indicates an objective response rate of 29% when both treatment arms are combined.

Capecitabine as a single agent also has demonstrated antitumor activity in patients refractory to anthracyclines and taxanes.[3] Further rationale for combining irinotecan with capecitabine is provided in part from xenograft studies of human A253 and FaDu head and neck tumors in nude mice. The investigators noted synergistic anticancer effects when irinotecan is given first, followed by a 24-hour delay before the start of capecitabine treatment.[28] These studies also demonstrated that doses lower than the maximum tolerated doses still produced maximal antitumor effects with cures being observed with the combination but not with single-agent treatment.[28]

To evaluate the effects of this potentially useful combination in refractory breast cancer, we have initiated a phase I trial of capecitabine/irinotecan in patients with metastatic or inoperable solid tumors.[29] The trial was based upon the animal xenograft data in that irinotecan is administered first, and then, after a 24-hour delay, the capecitabine is initiated. Irinotecan is given as a rapid intravenous injection once every 2 weeks, as this schedule is less likely to cause gastrointestinal toxicity than a weekly schedule. The capecitabine is administered daily for only 1 week with a washout phase of 7 days to allow any hyperbilirubinemia (seen in 18% of patients treated with this agent)[4] to resolve before the next irinotecan injection.

Patients receive irinotecan at 100 mg/m² IV on days 1 and 15, and oral capecitabine at 500 to 1,250 mg/m² twice daily on days 2 to 8 and 16 to 22, every 28 days. For the first 16 patients enrolled, the mean age is 61 years; 13 had prior chemotherapy (with an average of two prior chemotherapy courses) and 4 had prior radiation therapy. Suggested phase I dosing has yet to be determined, but it is expected that the maximum tolerated dose will be at or above the static irinotecan dose. The major toxicities to date have been leukopenia at day 8 and manageable gastrointestinal adverse events. Activity of the combination has been observed at all dose levels.[29] We believe that this combination needs further evaluation in breast cancer and gastrointestinal malignancies.

**Docetaxel/Epirubicin/Capecitabine Combination**

The potential benefits of a docetaxel/epirubicin/capecitabine combination are suggested by the preclinical synergy demonstrated with docetaxel/epirubicin in MCF7 breast cancer cell lines using the median effects model (Figure 4).[30,33] A phase II trial of this triplet in patients with locally advanced or metastatic breast cancer has been reported in abstract form.[31] Patients were aged 18 to 70 years, with Eastern Cooperative Oncology Group performance status 0 to 2, and no prior treatment for metastatic disease. Exclusion criteria included prior docetaxel treatment; anthracycline treatment within the prior 6 months; prior doxorubicin > 240 mg/m², epirubicin > 480 mg/m², or mitoxantrone > 70 mg/m²; cardiac disease; or history of grade 2 or greater neuropathy. Patients received oral capecitabine at 1,000 mg/m² twice daily on days 1 to 14, docetaxel at 75 mg/m² IV on
day 1, and epirubicin at 75 mg/m² IV on day 1, every 21 days. Among the 67 patients entered, the median age was 53 years and median performance status was 0; 51% had locally advanced cancer and 30% had received prior chemotherapy, with 16% having received prior anthracycline treatment. In the total group, 65 patients were evaluable for toxicity and 50 patients for response. The major response rate was 81% in locally advanced patients and 71% in metastatic disease patients. Further divisions of the responses are shown in Figure 5.[31]

Neutropenia (grades 3/4) was the predominant toxicity, occurring in 46% of patients. Of the 65 patients, 15% had febrile neutropenia. Asthenia was seen in six patients, mucositis in three, hand-foot syndrome in two, nausea and vomiting in six, and diarrhea in two. As this combination demonstrates significant activity in both locally advanced and metastatic disease, the triplet is currently in phase III trials and also needs to be evaluated in treatment of earlier disease.

Conclusions

The most mature study in advanced breast cancer demonstrated that the capecitabine/docetaxel combination has shown a significant advantage in tumor response and in disease-free and overall survival in anthracycline-pretreated patients. Based upon preclinical studies, numerous rational combinations of capecitabine with other active agents in breast cancer are in development. Many of these combinations have already shown early promise, while other regimens remain in early feasibility trials. Of the combinations tested to date, toxicity has generally been very manageable. In some cases, particularly the docetaxel/epirubicin/capecitabine combination, there is evidence to suggest that capecitabine combinations should be evaluated in earlier-disease settings. Capecitabine, as a single agent and in combination with docetaxel, has recently been introduced into breast adjuvant trials. Additional preclinical studies, both in tissue culture and in xenograft model systems, suggest that in human trials the combination of capecitabine and EGFR inhibitors, including HER2/neu inhibitors, may offer enhanced therapeutic efficacy in both EGFR or HER2/neu-positive breast tumors and in other tumors over-expressing these receptors.

References:


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