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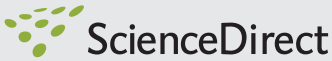

Capecitabine and docetaxel in the treatment of metastatic breast cancer: combination, sequence or single agent?

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ABSTRACT

Capecitabine is preferentially activated to 5-fluorouracil in tumour tissue by thymidine phosphorylase (TP). When combined with agents known to upregulate TP, such as docetaxel, a synergistic interaction was noted in preclinical models. In a phase III clinical trial, the combination of capecitabine plus docetaxel yielded improved response rates, progression-free survival and an absolute survival benefit of 3 months compared with docetaxel alone. Combination therapy was associated with significantly more diarrhoea, stomatitis, hand–foot syndrome and nausea and vomiting, although dose reductions can reduce these side-effects while maintaining a survival benefit. The superiority of the combination as opposed to the sequential use of these drugs remains unclear. There is interest in developing single-agent capecitabine as first-line treatment for patients with more indolent disease where, as a consequence of improved tolerability, continued use may lead to improvements in overall survival.

1. Introduction

Combination chemotherapy is commonly used in the treatment of metastatic breast cancer (MBC), though in the palliative setting the advantage of this approach as opposed to the sequential use of single agents is perhaps less clear. In considering what constitutes an ideal combination of cytotoxic agents there are a number of factors that should be considered. Each agent should have its own activity and there should preferably be some evidence of synergy. Most importantly, the toxicities of the agents should preferably not overlap. In practice, few chemotherapy combinations meet all of these criteria (e.g. toxicities, such as myelosuppression and mucositis, frequently overlap).

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2. Capecitabine plus docetaxel

Capecitabine is an orally bioavailable drug activated by a cascade of enzymes culminating in conversion to 5-fluorouracil by thymidine phosphorylase (TP). While TP is known to be upregulated in cancers,[1,2] it can also be upregulated by other chemotherapy agents (e.g. gemcitabine, docetaxel) and radiotherapy.[3,4] Preclinical synergy between capecitabine and docetaxel was demonstrated in the late 1990s. When used as single agents, capecitabine and docetaxel slowed tumour growth, but when combined the two agents produced a reduction in tumour burden that was the result of a synergistic effect.[5] This was not associated with an additive effect in toxicity. As a result of this work, and given the relative lack of myelosuppression associated with capecitabine, this combination was taken forward into the clinical setting.

O'Shaughnessy et al. conducted a trial comparing capecitabine (1250 mg/m^2 twice a day for 2 weeks of every

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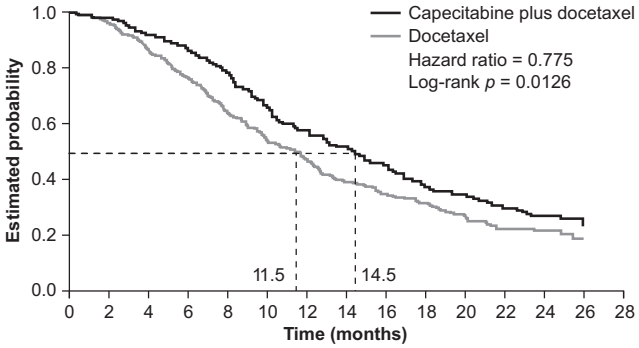

Fig. 1 – A comparison of overall survival between the capecitabine plus docetaxel combination arm and docetaxel alone arm in anthracycline-pretreated metastatic breast cancer patients in the O'Shaughnessy trial. Originally published by the American Society of Clinical Oncology (O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;20:2812–23).

3-week cycle plus docetaxel 75 mg/m^2 on day 1) with docetaxel alone (100 mg/m^2 on day 1) as first-, second- or third-line therapy for MBC. [6] The primary endpoint was progression-free survival (PFS).

The activity of the combination was significantly greater, achieving a response rate of 42% compared with 30% in the docetaxel-alone arm ($p = 0.006$), and a 2-month increase in PFS ($p = 0.0001$). This translated into an absolute survival benefit of 3 months for the combination ($p = 0.0126$) (see Fig. 1), despite the lower dose of docetaxel used in the combination arm. This confirmed the preclinical results with a demonstrable improvement in overall survival, and was one of the first trials to demonstrate a survival benefit of this extent in a combination chemotherapy regimen in advanced-stage breast cancer.

A *post hoc* analysis of this study demonstrated that even in patients with a relatively poor prognosis (those with an initial disease-free interval of <2 years), the benefits of the combination were still evident ($p = 0.013$). [7]

Patients receiving the combination had greater toxicity in terms of diarrhoea, stomatitis, hand–foot syndrome and nausea and vomiting. However, there was more febrile neutropenia, myalgia, arthralgias and pyrexias in the docetaxel-alone arm, presumably attributable to the fact that docetaxel was administered at a higher dose than in the combination arm. Therefore, there is a trade-off in terms of side-effects between the two treatment regimens. Global health status estimates from this study demonstrated that quality of life was not significantly different between the two arms of the trial.

3. Dose reduction

The projected dose intensity was, however, difficult to deliver. In approximately half of the cases treated the dose was reduced to 75% for one or, most commonly, both drugs, and in a significant minority of patients the dose of capecitabine was reduced to 50%. Reassuringly, a *post hoc* analysis demonstrated that if the dose of the second course was reduced then overall survival was not significantly compromised compared with continuing on the full-dose regimen. Leonard et al. found that reducing the dose of capecitabine reduced the occurrence of higher grades of diarrhoea, stomatitis and hand–foot syndrome, and, when the dose of docetaxel was reduced as well, febrile neutropenia. Nevertheless, a survival benefit was still observed. [7]

These data were presented to the UK National Institute for Clinical Excellence, which approved the combination based on improvements in response rate, time to disease progression and survival. Pharmacoeconomics were also considered and the combination was found to be cost effective, since the cost of capecitabine was largely offset by the reduced acquisition cost of docetaxel.

4. Sequential use of docetaxel and capecitabine

The pivotal trial cited above did not address the clinically important question of whether the combination of capecitabine plus docetaxel was superior to the planned sequence of docetaxel followed by capecitabine. This is an important consideration since several studies have demonstrated that the activity of capecitabine as a single agent following docetaxel failure produces a response rate in the order of 20%. [8–11] In the O'Shaughnessy study, patients who received capecitabine upon docetaxel failure (>25%) had significantly greater survival rates than patients who received other types of chemotherapy ($p = 0.005$) (see Fig. 2). [12]

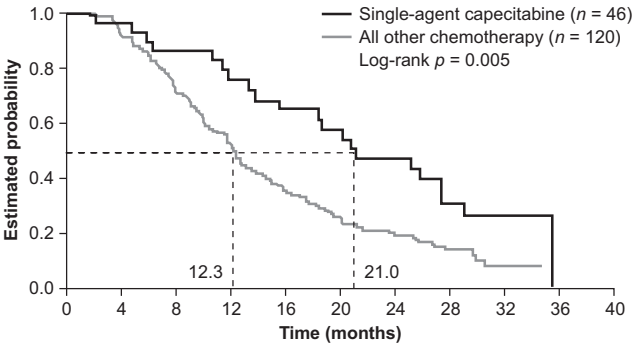

Fig. 2 – A comparison of capecitabine monotherapy versus all other chemotherapy following docetaxel failure in metastatic breast cancer patients in the *post hoc* analysis of the O'Shaughnessy trial. [12]

A small randomised study ($n = 100$) compared the planned sequence of docetaxel (100 mg/m^2) followed at relapse by capecitabine (1250 mg/m^2) versus a capecitabine (1250 mg/m^2) plus docetaxel (75 mg/m^2) combination as first-line therapy for MBC patients who had received prior anthracycline treatment. [13] Response rates were significantly higher in the combination arm versus the sequential arm (68% vs. 40%, $p = 0.004$). There were also significant improvements in time to disease progression ($p = 0.001$) and overall survival ($p = 0.006$) in the combination arm. While this study supports the use of combination therapy with capecitabine plus docetaxel, additional supporting data would be reassuring.

5. Capecitabine as first-line treatment

Capecitabine has been considered for use as monotherapy for first-line chemotherapy of metastatic disease. Two small studies explored this: Talbot et al. compared capecitabine with paclitaxel, and O'Shaughnessy et al. compared capecitabine with the combination of cyclophosphamide plus methotrexate plus 5-fluorouracil (CMF). Response rates and time to disease progression were not significantly different when capecitabine was compared with the more conventional regimens, though the small size of the studies prevents any firm conclusions from being made. [14,15]

In a randomised phase II trial comparing capecitabine 1250 mg/m^2 with capecitabine 1000 mg/m^2 as first-line chemotherapy in an older group of patients (aged 65–89 years) with advanced breast cancer, encouraging response rates of 37% and 35%, respectively, were noted, with a low incidence of grade 3/4 toxicities. [16]

In a head-to-head comparison of single-agent capecitabine versus the capecitabine plus docetaxel combination as first-line chemotherapy, the Mexican Oncology Study Group studied capecitabine 1250 mg/m^2 as a single agent followed on disease progression by a taxane, and compared it with the combinations of capecitabine 825 mg/m^2 plus docetaxel 75 mg/m^2 and capecitabine 825 mg/m^2 plus paclitaxel 175 mg/m^2 in anthracycline-pretreated MBC patients ($n = 345$). [17] PFS and overall survival (median 24 months) were comparable between treatments, and time to treatment failure was approximately 9 months in all of the arms.

More recently, Stockler et al. compared intermittent (1000 mg/m^2) and continuous (650 mg/m^2) administration of capecitabine versus CMF. [18] The response rates and PFS times were equivalent in the three arms of the study. Median PFS was 6 months in the combined capecitabine arms and 7 months in the CMF arm. Despite this, an improvement in survival was noted in the combined capecitabine arms compared with the CMF arm (22 vs. 18 months). In this study, nearly 20% of patients were still receiving capecitabine at 12 months whereas only 5% were still receiving CMF therapy, even though the intention was to treat until disease progression. Hence the difference in median survival observed between both of the capecitabine arms and the CMF arm is probably attributable to the fact that, as a result of improved tolerability, responding patients were able to continue on capecitabine for longer than on CMF.

In terms of adverse events, an increased incidence of hand–foot syndrome was observed with the low-dose continuous and intermittent capecitabine schedules ($p < 0.0001$), whereas CMF was associated with excess neutropenia, febrile neutropenia and stomatitis ($p < 0.0001$).

The ability to continue capecitabine as a consequence of its tolerability might also explain the most recent data from the CHAT (Capecitabine, Herceptin and Taxotere) study, which investigated whether the capecitabine plus docetaxel combination could be combined successfully with trastuzumab in human epidermal growth factor receptor 2-positive patients. The study compared the combination of capecitabine plus docetaxel plus trastuzumab with docetaxel plus trastuzumab. Although response rates to the triplet combination and doublet combination regimens were similar, PFS was significantly higher in patients receiving the triplet combination. The endpoint of median survival has not been reached in either arm of the study. [19]

6. Conclusions

The capecitabine plus docetaxel combination has been shown to yield better response rates, time to progression and overall survival than single-agent docetaxel. However, attention must be paid to dose reduction and the fact that, perhaps due to relatively poor tolerability at the licensed doses, few clinicians in the UK and Europe use this combination.

Those patients likely to be selected for this combination might include patients with a good performance status who nevertheless have visceral disease in which maximal opportunity for reduction in tumour burden is required, and where, necessarily, the likelihood of second-line treatment might be low.

Biological treatments have perhaps set new benchmarks for the treatment of MBC. Trastuzumab provides a 7–9 month survival benefit and does not add greatly to toxicity. [20] This magnitude of benefit has not been noted for combination chemotherapy, and where palliation is an important aim, the use of single-agent capecitabine, particularly in an era of adjuvant taxanes, deserves consideration. Capecitabine might be a valid choice as a single agent in patients with indolent disease, older patients or patients who do not want to suffer hair loss and the side-effects of other chemotherapies. To what extent its use as a single agent in patients with more aggressive or visceral

disease might compromise outcome has not yet been adequately evaluated.

Conflict of interest statement

Dr Miles has been in receipt of honoraria for invited presentations and advisory boards for Roche, Eli Lilly and Company, and sanofi-aventis.

References

1. Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998;**34**:1274–81.
2. Schüller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumour following oral administration to colorectal cancer patients. *Cancer Chemother Pharmacol* 2000;**45**:291–7.
3. Ishitsuka H. Capecitabine: preclinical pharmacology studies. *Invest New Drugs* 2000;**18**:343–54.
4. Sawada N, Fujimoto-Ouchi K, Ishikawa T, et al. Antitumour activity of combination therapy with capecitabine plus vinorelbine, and capecitabine plus gemcitabine in human tumour xenograft models. *Proc Am Assoc Cancer Res* 2002 [abstract 5388].
5. Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by Taxol/Taxotere in human cancer xenografts. *Clin Cancer Res* 1998;**4**:1013–19.
6. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002;**20**:2812–23.
7. Leonard R, Miles D, Reichardt P, et al. Optimizing the management of HER2-negative metastatic breast cancer with capecitabine (Xeloda). *Semin Oncol* 2004;**31**(Suppl 10):21–8.
8. Blum JL, Dieras V, Lo Russo PM, et al. Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *Cancer* 2001;**92**:1759–68.
9. Reichardt P, Von Minckwitz G, Thuss-Patience PC, et al. Multicenter phase II study of oral capecitabine (Xeloda) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. *Ann Oncol* 2003;**14**:1227–33.
10. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. *Eur J Cancer* 2004;**40**:536–42.
11. Maung K, O'Shaughnessy JA, Sledge GW Jr. Capecitabine/bevacizumab compared to capecitabine alone in pretreated metastatic breast cancer: results of a phase III study. *Clin Breast Cancer* 2003;**3**:375–7.
12. Miles D, Vukelja S, Moiseyenko V, et al. Survival benefit with capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase III trial. *Clin Breast Cancer* 2004;**5**:273–8.
13. Beslija S, Obralic N, Basic H, et al. A single institution randomized trial of Taxotere (T) and Xeloda (X) given in combination vs. Taxotere (T) followed by Xeloda (X) after progression as first line chemotherapy (CT) for metastatic breast cancer (MBC). *Eur J Cancer Suppl* 2005;**3**:118 [abstract 407].
14. Talbot DC, Moiseyenko V, Van Belle S, et al. Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines. *Br J Cancer* 2002;**86**:1367–72.
15. O'Shaughnessy JA, Blum J, Moiseyenko V, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol* 2001;**12**:1247–54.
16. Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol* 2005;**23**:2155–61.
17. Soto C, Torrecillas L, Reyes S, et al. Capecitabine (X) and taxanes in patients (pts) with anthracycline-pretreated metastatic breast cancer (MBC): sequential vs combined therapy results from a MOSG randomized phase III trial. *J Clin Oncol* 2006;**24**(Suppl) [abstract 570].
18. Stockler MR, Sourjina T, Grimison P, et al. A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC). *J Clin Oncol* 2007;**25**(Suppl) [abstract 1031].
19. Wardley A, Antón-Torres A, Pivot X, et al. Evaluation of trastuzumab, docetaxel and capecitabine as first-line therapy for HER2-positive locally advanced or metastatic breast cancer. *Breast Cancer Res Treat* 2007;**106**(Suppl 1):S33 [abstract 309].
20. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;**23**:4265–74.