Dosage of Capecitabine and Cyclophosphamide Combination Therapy in Patients with Metastatic Breast Cancer

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Abstract. Background: Capecitabine is a highly effective and well-tolerated treatment for metastatic breast cancer (MBC) and extends survival when combined with docetaxel. Capecitabine and cyclophosphamide are orally administered and have preclinical synergy and non-overlapping toxicities. Patients and Methods: Sixteen pretreated MBC patients received escalating doses of oral capecitabine 628 to 829 mg/m² twice daily (bid) plus oral cyclophosphamide 33 to 50 mg/m² bid, on days 1 to 14 every 21 days. Results: Among the ten patients receiving capecitabine/cyclophosphamide 829/33 mg/m² bid on days 1 to 14, two experienced dose-limiting toxicities (DLT, treatment delay >1 week due to grade 2 leukopenia). Because neither patient developed further grade >1 toxicity and none of the patients experienced grade 3/4 toxicities or further DLTs, this dose level is the recommended regimen, producing partial responses in two of five evaluable patients. Conclusion: The recommended all oral capecitabine/cyclophosphamide combination regimen is well tolerated and active in MBC, and is being evaluated in a phase II study in anthracycline-pretreated MBC.

Anthracycline- or taxane-based regimens are standard chemotherapies for metastatic breast cancer (MBC). However, hair loss associated with both anthracycline and taxane therapy is distressing for women and can lead patients to consider stopping therapy (1). Intense nausea associated with anthracycline-based therapy also adversely affects patients’ quality of life (2). Therefore a chemotherapy regimen that minimises these effects is likely to be attractive to patients. Another important consideration with taxane- and anthracycline-based therapies is the need for regular clinic visits or hospitalisations for intravenous administration of chemotherapy, which are inconvenient and disruptive. The majority of patients prefer oral to intravenous chemotherapy, providing efficacy is not compromised (3-5). In patients with a strong preference for oral therapy or a fear of needles, patients in whom venous access is problematic, or those who have difficulty in regularly attending a cancer centre for intravenous therapy, active oral therapy is appealing. The combination of capecitabine and cyclophosphamide potentially provides an attractive, all oral alternative, giving patients more freedom and a sense of control over their treatment.

Both cyclophosphamide and capecitabine have demonstrated efficacy in breast cancer in a range of settings. Cyclophosphamide is typically used as a component of combination regimens, such as AC (doxorubicin and cyclophosphamide) and fluoropyrimidine-based combination regimens including CMF (cyclophosphamide, methotrexate and 5-fluorouracil (5-FU)). Capecitabine monotherapy has shown excellent efficacy and safety in pretreated MBC (6-9) and as first-line monotherapy (10). The high single-agent activity and unique safety profile of capecitabine, including a particularly low incidence of myelosuppression and absence of alopecia, provide a strong rationale for incorporating capecitabine into combination regimens. In addition, the

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crucial role of intratumoral thymidine phosphorylase (TP) in the activation of capecitabine to 5-FU (11) makes capecitabine a logical combination partner for therapies that up-regulate TP. Several chemotherapeutic agents, including cyclophosphamide, docetaxel and paclitaxel, up-regulate intratumoral TP and have demonstrated synergistic antitumour activity in combination with capecitabine, providing a clear rationale for these combinations in the clinical setting (12, 13). Randomised clinical trials have already demonstrated that the addition of capecitabine to docetaxel significantly improves response rate, time to progression and overall survival compared with docetaxel alone in anthracycline-pretreated patients (14) and compared with sequential docetaxel followed by capecitabine as first-line therapy (15).

Based on the good tolerability, low incidence of alopecia and oral administration of cyclophosphamide and capecitabine, together with their preclinical synergy, a dosage study was conducted to evaluate the safety and efficacy of an all oral combination of capecitabine and cyclophosphamide in patients with MBC and to determine the optimum dosing schedule.

Patients and Methods

Eligibility. Eligibility criteria included: histologically or cytologically confirmed MBC; age 20 to 74 years; ECOG Performance Status 0 to 2; at least one prior chemotherapy regimen in the adjuvant or metastatic setting; resolution of all toxicities from prior therapy; adequate vital organ functions (serum haemoglobin concentration ≥9.0 g/dl, neutrophil count ≥2,000/mm³, platelet count ≥100,000/mm³, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <1.5 x upper normal limit (UNL) of range set by the institution (in cases of hepatic metastasis, ≤3 x UNL, alkaline phosphatase ≤2.5 x UNL, serum creatinine <1.5 x UNL, serum total bilirubin <1.25 x UNL, and normal electrocardiogram)); creatinine clearance >50 ml/min; life expectancy ≥3 months; no symptomatic central nervous system metastases and no infectious complications. All patients provided written informed consent.

Treatment plan. Patients received up to six 3-week cycles of capecitabine and cyclophosphamide administered orally twice daily (bid) on days 1 to 14, followed by a drug-free interval from day 15 to day 21. Three escalating dose levels were planned: level 1 (capecitabine/cyclophosphamide: 628/33 mg/m² bid); level 2 (capecitabine/cyclophosphamide: 829/33 mg/m² bid); level 3 (capecitabine/cyclophosphamide: 829/50 mg/m² bid).

Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0 (16). Dose-limiting toxicities (DLT) were defined as any of the following during the first two cycles of therapy: grade 4 neutropenia lasting ≥7 days; platelet count <25,000/mm³; fever ≥38°C lasting ≥72 hours; grade 3 neutropenia with mucositis or diarrhoea grade ≥2; grade 3 or 4 non-haematological toxicity (excluding alopecia, nausea and vomiting, unless nausea and/or vomiting made oral feeding impossible for ≥4 days, necessitating fluid infusion) and any event leading to a >7-day delay in administration of the next cycle.

The maximum tolerated dose (MTD) was determined by assessing safety during the first two cycles. In the event of safety concerns at dose level 1, patients would be enrolled at dose level -1 (capecitabine/cyclophosphamide: 502/33 mg/m² bid). If no DLTs occurred in the first three patients, the dose would be increased to the next level. If only one of the three patients experienced a DLT, three additional patients would be treated at that dose level, and in the absence of further DLTs the dose would be escalated to the next level. If DLTs occurred in two or more of a cohort of six patients, this dose would be considered the MTD. If only three patients had been treated at the preceding dose level, three additional patients would be treated at the preceding dose level to confirm the recommended dose (RD). If the MTD was not reached at dose level 3, level 3 would be considered the RD.

Dose modifications. From cycle 3 onwards, capecitabine and cyclophosphamide treatment would be interrupted if patients experienced haematological or non-haematological toxicity (excluding hand-foot syndrome (HFS) grade >2) or grade 3 HFS. In patients experiencing a grade 2 adverse event, treatment would be withdrawn and resumed at the same dose only when symptoms resolved to grade 0 or 1. If a grade 3 toxicity occurred, treatment would be interrupted until symptoms resolved to grade 0-1 and then treatment would be resumed at 75% of the previous dose. If a grade 4 toxicity occurred, treatment would be discontinued permanently. If treatment was interrupted for >3 weeks, the patient would be withdrawn from the study.

Study assessments. The following tests were conducted within two weeks prior to the start of chemotherapy and every week during the first two treatment cycles: general haematology, blood chemistry and physical examination for other subjective and objective symptoms/clinical findings. During cycles 3 to 6, these tests were conducted immediately before each treatment cycle and at the study end. The performance status was evaluated before starting each treatment cycle and at the study end. Adverse events were monitored and recorded throughout the treatment (NCI CTC). The tumour status was monitored four weeks prior to the start of treatment, before the start of cycles 3 and 5, and at the end of treatment, using chest X-ray, computed tomography (CT) and magnetic resonance imaging (MRI), evaluation of serum tumour markers, and relevant ultrasound examination and bone scintography (if possible). The tumour response was determined using the Response Evaluation Criteria in Solid Tumors (RECIST) (17).

Results

Patient characteristics. Between August 2003 and February 2004, nine patients (six at dose level 1, three at dose level 2) were enrolled. To confirm the tolerability of dose level 2, seven additional patients were enrolled between August 2004 and February 2005. Thus, a total of 16 patients participated in the phase II study to determine the RD.

Table I shows patient characteristics. All patients had performance status 0. The median age was 55 years (range: 43 to 70). The major metastatic sites were lymph nodes, lungs and liver. The majority of patients had received two
or more prior chemotherapy regimens; six out of the nine patients treated in the dose-escalation phase had received three or more prior regimens.

**DLTs.** Cycle 2 was delayed by one week in two out of the six patients treated at dose level 1 due to grade 2 leukopenia. However, no DLTs occurred in any of these patients. Two out of the three patients treated at dose level 2 developed DLTs. Treatment was interrupted for ≥1 week for each of the patients because of grade 2 leukopenia, which did not resolve to grade 0-1 within seven days. Both patients had been heavily pretreated (three or more prior regimens). Only one of these patients experienced grade ≥3 haematological toxicity (grade 3 neutropenia) and neither developed any grade >1 non-haematological toxicity. Based on these findings, the Data and Safety Monitoring Committee agreed that dose level 2 should not be defined as the MTD and recommended protocol modification. Consequently treatment was delayed only if patients had a neutrophil count ≥1,500/mm³, a platelet count ≥75,000/mm³, or haemoglobin ≥8.0g/dl. Dose level 2 was expanded to confirm its tolerability.

Seven additional subjects were enrolled at dose level 2. Two patients were excluded because safety evaluation was not possible (one withdrew consent and data were missing for the other). No DLTs occurred during the first two cycles in any of these five subjects, and none developed any grade ≥3 haematological toxicity or grade ≥2 non-haematological toxicity. Consequently dose level 2 (capecitabine 829 mg/m² bid plus cyclophosphamide 33 mg/m² bid) was confirmed as well tolerated.

**Safety.** Table II lists toxicities by dose level. There were no grade 2, 3 or 4 non-haematological events at any of the dose levels. During the early cycles, the neutrophil count fell to nearly 1,500/mm³, but then remained stable, indicating that continued therapy did not exacerbate toxicity. Excluding the two patients with DLTs, seven out of the eight patients treated at the RD completed all six treatment cycles. The remaining patient withdrew consent after only one cycle. No further treatment interruptions were required and there were no dose reductions. All patients were treated as out-patients.

**Efficacy.** Two out of the eight evaluable patients achieved partial responses. Both of these patients were treated at dose level 2, giving a response rate of 40% in the five evaluable patients treated at the RD. Both of these patients received capecitabine/cyclophosphamide as first-line chemotherapy. Disease progression was recorded at the end of the sixth cycle in both patients. Previous treatment in all five evaluable patients treated at the RD is shown in Table III.

**Discussion**

This study identified dose level 2 (capecitabine 829 mg/m² bid plus cyclophosphamide 33 mg/m² bid on days 1 to 14 of each 3-week cycle) as the RD. As expected given the relatively low dose of capecitabine in this study, the incidence of HFS was low. Only one patient experienced grade 1 HFS during the
first two cycles, with an additional case occurring during a subsequent cycle. There were no grade ≥2 non-haematological toxicities, only one patient experienced AST elevation (grade 1) and there were no bilirubin elevations. This contrasts with the safety profile of capecitabine monotherapy observed in two phase II studies in breast cancer conducted in Japan. In both studies, capecitabine 828 mg/m² was given twice daily, days 1 to 21 of each 4-week cycle (18, 19). Grade 3/4 bilirubin elevations were reported in 8% of patients in one study and 22% in the other.

In a phase I study investigating capecitabine/cyclophosphamide combination therapy in patients with advanced cancer (20), grade 3 diarrhoea and grade 4 vomiting were dose limiting. This marked difference in the safety profile of the combination is probably attributable to the different dosing schedule used by Findlay et al. (20), with capecitabine administered every day without interruption and cyclophosphamide administered on days 1 to 14 every four weeks. Therefore the dose intensity of both drugs was substantially higher than in the present study.

Interestingly, cyclophosphamide has been evaluated in combination with doxifluridine, an intermediate metabolite of capecitabine, in a phase II study in patients with MBC (21). The overall response rate was 60% and the median time to progression and overall survival were 11.7 and 40.3 months, respectively. Grade 3/4 haematological toxicity occurred in 22% and non-haematological toxicity occurred in 5% of patients. In a phase III trial in the adjuvant setting, the addition of cyclophosphamide to doxifluridine significantly improved disease-free survival compared with doxifluridine alone, but resulted in a significantly higher rate of toxicity (22). In the present study, replacing doxifluridine with capecitabine as a combination partner for cyclophosphamide appeared to improve tolerability. Particularly noteworthy was the lack of non-haematological toxicities of grade >1 severity.

Two out of the five evaluable patients treated at the RD achieved a partial response. Therefore further evaluation is warranted, particularly as a pharmacokinetic study has demonstrated that the 5’-deoxy-5-fluorouridine (5’-DFUR) area under the blood concentration curve was 2.4-fold greater for capecitabine 828 mg/m² twice daily than for doxifluridine 400 mg three times daily (23). It is plausible that capecitabine/cyclophosphamide may improve the efficacy of cyclophosphamide/fluoropyrimidine therapy as well as the tolerability compared with doxifluridine/cyclophosphamide.

This study suggests that the all oral regimen of capecitabine 829 mg/m² twice daily plus cyclophosphamide 33 mg/m² twice daily, both administered on days 1 to 14 every three weeks, is feasible, active and extremely well tolerated.

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**References**

References


