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# Future treatment options with capecitabine in solid tumours

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**Abstract**

The oral fluoropyrimidine, capecitabine is attracting great interest in the context of tumour-selective therapy and rationally designed combination regimens. Agents such as taxanes upregulate thymidine phosphorylase (TP), and there is therefore a clear rationale for their combination with capecitabine. Preclinical studies of capecitabine/taxane combination therapy demonstrated synergistic antitumour activity and phase I studies showed encouraging efficacy. Therefore, a randomised, phase III trial (docetaxel versus docetaxel/capecitabine) has been initiated in anthracycline-refractory metastatic breast cancer patients. Recruitment is complete. In colorectal cancer, capecitabine/oxaliplatin combination therapy is promising and a phase I, dose-finding trial has been conducted in patients with refractory metastatic solid tumours. A similar trial has evaluated capecitabine/irinotecan combination treatment. Capecitabine is also being investigated as adjuvant therapy for colorectal and breast cancers. The primary objective of the ongoing X-ACT trial in almost 2000 Dukes' C colon cancer patients is to demonstrate at least equivalent disease-free survival between capecitabine and the Mayo Clinic regimen. In addition, the CALGB is planning a randomised, phase III trial of capecitabine versus doxorubicin/cyclophosphamide or cyclophosphamide/methotrexate/5-fluorouracil (CMF) as adjuvant treatment in high-risk, node-negative breast cancer patients aged >65 years. © 2002 Published by Elsevier Science Ltd.

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## 1. Introduction

Several clinical studies have shown that the rationally designed, tumour-selective, oral fluoropyrimidine derivative capecitabine is an effective and well tolerated treatment for colorectal and breast cancer patients [1–4]. In addition, oral capecitabine offers a convenient, patient-orientated treatment option. Most patients prefer an orally administered agent [5,6] and this route of administration avoids the complications and inconvenience associated with central venous access and portable pumps.

Following oral administration, capecitabine is converted via a three-step enzymatic pathway to 5-fluorouracil (5-FU). The last activation step to 5-FU is catalysed by thymidine phosphorylase (TP), an enzyme that is highly expressed in tumour tissue, is associated with tumour angiogenesis and has shown anti-apoptotic properties [7]. It has been shown that high expression of TP is associated with resistance to conventional 5-FU treatment in various gastrointestinal tract tumours, particularly colon cancer [8,9]. Consequently, capecitabine potentially offers a means of overcoming this type of resistance. Furthermore, data from human tumour xenografts have shown that the ratio of TP to dihydropyrimidine dehydrogenase, the rate-limiting catabolising enzyme for fluoropyrimidines, can be used to predict response to capecitabine [10]. This may provide a basis for the development of patient-specific treatment, enabling the identification of patients less likely to benefit from capecitabine based on biochemical targets. Consequently, capecitabine is attracting great interest for further development in the context of tumour-selective therapy and rationally designed combination regimens.

## 2. Capecitabine plus chemotherapy in metastatic disease

Preclinical studies in xenograft models of colorectal cancer have shown that administration of several cytotoxic agents, including taxanes, mitomycin C and cyclophosphamide, leads to an increase in TP concentrations

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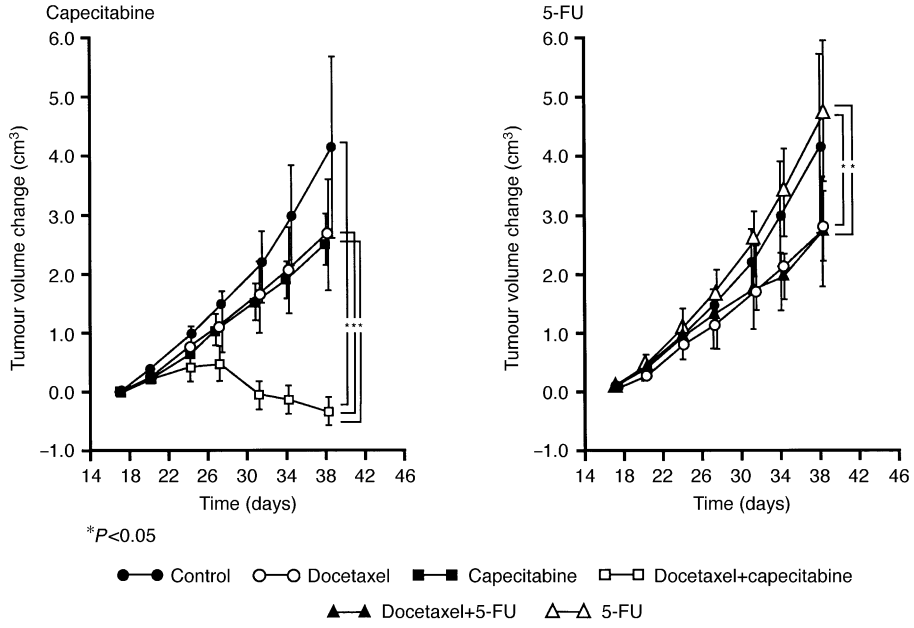


Fig. 1. Capecitabine plus taxanes in MX-1 breast cancer xenografts [11].

in tumour tissue [11,12]. Furthermore, a study in MX-1 breast cancer xenografts demonstrated that the efficacy of either paclitaxel or docetaxel in combination with capecitabine was synergistic (Fig. 1). In contrast, paclitaxel in combination with either 5-FU or uracil plus tegafur (UFT) showed only additive activity. The authors concluded that paclitaxel and docetaxel might enhance the efficacy of capecitabine by upregulating TP activity in tumour tissues.

### 2.1. Capecitabine plus taxanes in breast cancer

The preclinical observations reported above have provided the rationale for several clinical trials exploring TP-upregulating agents such as taxanes in combination with capecitabine. Capecitabine and the taxanes paclitaxel and docetaxel have proven efficacy in the treatment of breast cancer. In addition, the mechanism of action of these agents is clearly distinct with no overlap of key toxicities.

Pronk and colleagues [13] reported a phase I study of capecitabine plus docetaxel combination treatment in 33 therapy-refractory solid tumour patients. The most common tumour types were colorectal ($n=9$), adenocarcinoma of unknown primary ($n=6$) and breast ($n=3$). All patients had a Karnofsky Performance Score $\geqslant 70\%$. Patients received docetaxel (75, 85 or 100 mg/m$^2$ as a 1-h infusion on day 1 every 3 weeks) plus oral capecitabine (825, 1000 or 1250 mg/m$^2$ twice daily on days 1–14 every 3 weeks (intermittent regimen)). One patient treated at the 825 mg/m$^2$ capecitabine plus 100 mg/m$^2$ docetaxel dose level experienced dose-limiting grade 3 nausea, and at the capecitabine 1000 mg/m$^2$ plus docetaxel 100 mg/m$^2$ dose level grade 3 septicaemia was dose limiting in one patient and all patients reported grade 2-3 asthenia, which was considered dose limiting. There were no dose-limiting toxicities in patients receiving docetaxel 75 mg/m$^2$ in combination with capecitabine 1000 or 1250 mg/m$^2$. Antitumour activity was observed in a range of tumour types, including two complete responses and three partial responses (2 breast cancer patients and 1 colon cancer patient). There was no evidence of a pharmacokinetic interaction between capecitabine and docetaxel. The results of this study indicated that two dose regimens are feasible: 100 mg/m$^2$ docetaxel plus 825 mg/m$^2$ capecitabine twice daily and 75 mg/m$^2$ docetaxel plus 1250 mg/m$^2$ capecitabine twice daily.

The second of these regimens has been selected for evaluation in an ongoing, randomised, phase III trial. This international trial is comparing capecitabine (1250 mg/m$^2$ twice daily, intermittent regimen) plus docetaxel (75 mg/m$^2$/day) versus docetaxel (100 mg/m$^2$/day) alone as second-line therapy in metastatic breast cancer patients who have failed anthracycline treatment. Recruitment for this study is now complete. Additional clinical studies are being conducted in metastatic breast cancer patients to investigate capecitabine in combination with vinorelbine, epirubicin/cyclophosphamide and docetaxel/epirubicin. Oral combination regimens are also in development including combinations of capecitabine with cyclophosphamide or idarubicin.

### 2.2. Capecitabine plus oxaliplatin in colorectal cancer

In the future, combination regimens are likely to play an increasingly important role in the treatment of colorectal cancer in an attempt to improve efficacy and, in

particular, survival. Several clinical trials have evaluated fluoropyrimidine regimens in combination with novel agents such as irinotecan and oxaliplatin, which led to their approval in Europe and/or the USA for first-line use in combination with fluoropyrimidines. Therefore, phase I trials have been undertaken to investigate combining these agents with capecitabine.

The combination of oxaliplatin plus capecitabine appears to be a very promising option for the treatment of colorectal cancer, particularly as the synergy seen between fluoropyrimidines and oxaliplatin can partly overcome clinical resistance to fluoropyrimidines. A multicentre, dose-finding, phase I trial has been conducted in 23 patients with refractory metastatic solid tumours [14]. Various capecitabine dose levels were explored (500, 825, 1000 and 1250 mg/m$^2$ twice daily, intermittent regimen) combined with oxaliplatin (130 mg/m$^2$/day, given intravenously (i.v.) on day 1), with each cycle repeated every 3 weeks. The dose-limiting toxicity was diarrhoea. Among 9 patients with pretreated colorectal cancer, partial responses occurred in 5 patients. The recommended dose level identified for further clinical development was capecitabine 1000 mg/m$^2$ twice daily (intermittent regimen) plus i.v. oxaliplatin 130 mg/m$^2$ on day 1 of each 3-week cycle. This regimen is being evaluated as first-line therapy for colorectal cancer in an international phase II study. In another dose-finding study conducted in Italy, in which the doses of both capecitabine and oxaliplatin were escalated, the regimen recommended for phase II evaluation was oxaliplatin 120 mg/m$^2$ on day 1 and capecitabine 1250 mg/m$^2$ twice daily on days 1–14, every 3 weeks, although the tolerability of this regimen still has to be confirmed [15]. Dose-limiting toxicities in this phase I trial were diarrhoea and stomatitis. In a recently reported, National Cancer Institute (NCI), phase I trial evaluating capecitabine in combination with oxaliplatin 130 mg/m$^2$ every 3 weeks in 32 patients with pretreated colorectal cancer, the combination demonstrated promising antitumour activity, even in patients with irinotecan-refractory disease [16].

### 2.3. Capecitabine plus irinotecan in colorectal cancer

A combination of irinotecan and prolonged application of capecitabine also appears to be promising in patients with colorectal cancer due to the single-agent activity of both drugs in this setting [17–19], the superior survival of irinotecan in combination with infusional fluoropyrimidines versus fluoropyrimidines alone demonstrated in phase III trials [19,20], and the lack of myelosuppression seen with capecitabine. Based on our experience with the combination of weekly irinotecan plus infused 5-FU [21], we initiated a phase I, single-centre trial in patients with advanced colorectal cancer [22]. Patients had measurable metastatic colorectal cancer, but had received no prior chemotherapy for their metastatic disease and had normal hepatic, renal and haematological function. In this trial, capecitabine 1000–1250 mg/m$^2$ twice daily, intermittent regimen, was combined with weekly irinotecan (70, 80 or 90 mg/m$^2$) six times repeated on day 50 (Table 1). To date, 37 patients have been treated, and a regimen of intermittent capecitabine 1000 mg/m$^2$ twice daily plus irinotecan 70 mg/m$^2$ is recommended for further evaluation in phase II/III studies.

In another study investigating capecitabine/irinotecan combination therapy, Cassata and colleagues [23] treated 35 patients with advanced colorectal cancer with two schedules of irinotecan (Arm A: 300 mg/m$^2$, day 1; Arm B: 150 mg/m$^2$, days 1 and 8) in combination with capecitabine (1250 mg/m$^2$ twice daily, on days 2–15) followed by a 1-week rest period. Responses were reported in 15 of 21 patients evaluable for response, including four complete responses. These first experiences indicated that the combination was feasible and active. To further improve the safety profile, the study is ongoing with irinotecan 240 mg/m$^2$ on day 1 in Arm A and 120 mg/m$^2$ on days 1 and 8 in Arm B, in combination with capecitabine 1000 mg/m$^2$ twice daily on days 2–15.

The trials described above suggest that for combination regimens comprising capecitabine with either irinotecan or oxaliplatin, the recommended dose of capecitabine appears to be between 900 and 1000 mg/m$^2$ twice daily for 14 days.

## 3. Capecitabine plus radiotherapy

The potential of capecitabine as a radiosensitiser in rectal cancer patients is also being investigated. 5-FU is a well-established radiosensitiser, with protracted infusion achieving superior efficacy to bolus infusion when combined with radiotherapy [24]. Preclinical data indicate that radiotherapy enhances the activity of TP, resulting in highly enhanced activity of capecitabine plus radiotherapy. In contrast, the combination of 5-FU plus radiotherapy produces only additive efficacy [25].

Table 1
Capecitabine plus irinotecan: phase I study [22]

| Level | Capecitabine (mg/m$^2$ twice daily) | Irinotecan (mg/m$^2$/day) | Patients *n* |
|---|---|---|---|
| 1 | 1000 | 70 | 3 (+13) |
| 2 | 1250 | 70 | 8 (+7) |
| 3 | 1250 | 80 | 6 |
| 4 | 1250 | 90 | |
| 5 | 1250 | 100 | |

Schedule: oral capecitabine on days 1–14 and 22–35; intravenous (i.v.) irinotecan on days 1, 8, 15, 22, 29 and 36 repeated every 50 days.

A phase I study of capecitabine plus radiotherapy has been conducted in patients with rectal cancer and 36 patients have received treatment to date [26]. Treatment comprises radiotherapy (1.8 Gy/day on 5 days/week up to 50.4 Gy plus boost S2–S5 5 Gy) plus oral capecitabine (250, 375, 500, 650, 825 or 1000 mg/m$^2$ twice daily) given from the first until the last day of radiotherapy. Preliminary results are encouraging: the combination is well tolerated with no grade 4 toxicities observed to date and it has shown antitumour activity. Furthermore, the capecitabine/radiotherapy combination treatment simplified chemoradiotherapy and was highly appealing to the patients. Capecitabine therefore has the potential to replace 5-FU as a radiosensitiser in the treatment of rectal cancer.

## 4. Use of capecitabine in the adjuvant setting

The role of capecitabine as adjuvant therapy in colorectal and breast cancers is also being investigated.

### *4.1. Adjuvant colorectal cancer*

The X-ACT trial, an open-label, phase III trial aiming to recruit 1956 patients with Dukes' C colon cancer, completed recruitment in September 2001 and is comparing bolus 5-FU/leucovorin (Mayo Clinic regimen) with capecitabine monotherapy (1250 mg/m$^2$ twice daily, intermittent regimen). The primary objective is to demonstrate at least equivalence in disease-free survival between the two regimens. Secondary endpoints of the study are overall survival, safety, quality of life (QoL) and health economics. Biochemical markers will also be measured in selected centres. Accrual was completed in September 2001.

### *4.2. Adjuvant breast cancer*

The Cancer and Leukemia Group B (CALGB) is finalising the design of a randomised, phase III trial of capecitabine versus doxorubicin/cyclophosphamide or cyclophosphamide/methotrexate/5-FU (CMF) for the adjuvant treatment of high-risk, node-negative breast cancer patients aged $>65$ years. The primary endpoint of the trial is 5-year relapse-free survival. Secondary endpoints include overall survival, QoL and physical function. In addition, treatment compliance, treatment tolerance and biological markers of response will be assessed.

## 5. Capecitabine monotherapy as first-line treatment for breast cancer

Two randomised, phase III trials are evaluating capecitabine monotherapy as first-line treatment for metastatic breast cancer. A three-arm trial is comparing capecitabine (intermittent or continuous regimen) with a CMF (Bonadonna) regimen. The more favourable of the two capecitabine regimens will be selected for further comparison with CMF in a two-arm extension phase of this large, phase III trial. A German phase III trial evaluating capecitabine as first-line therapy is in the planning stages.

## 6. Capecitabine in other tumour types

The activity of TP has been shown to be significantly higher in tumour tissue than in adjacent healthy tissue for a number of tumour types, including tumours of the stomach, cervix, uterus, ovary, kidney and bladder [27]. Therefore there is a clear rationale for exploring capecitabine therapy in other tumour types exhibiting high TP activity. A number of clinical studies of capecitabine in other tumour types are planned or in progress, including gastric, pancreatic, oesophageal, head and neck, ovarian, cervical, renal, prostate, hepatocellular and biliary tract cancers. The combination of capecitabine plus gemcitabine in pancreatic cancer appears particularly promising, and a phase III trial evaluating gemcitabine plus capecitabine versus gemcitabine alone will soon begin. Further studies will include evaluation of predictive markers, such as TP, in identifying patients most likely to benefit from capecitabine. Combination therapy studies with other tumour-selective therapies, such as trastuzumab in HER2-positive cancer patients, are also planned.

## 7. Conclusions

A number of clinical trials have indicated that the oral, tumour-selective fluoropyrimidine capecitabine is effective and well tolerated given either as monotherapy or in combination with traditional or novel cytotoxic agents in both colorectal and breast cancers. In addition, the unique, tumour-targeted mechanism of action of capecitabine may overcome certain forms of resistance to other fluoropyrimidines. Capecitabine is therefore likely to be a valuable component of future drug combinations owing to its documented single-agent activity and favourable safety profile.

In addition to the developments with capecitabine in patients with colorectal and breast cancers, in both the metastatic and adjuvant settings, a range of clinical studies in other tumour types is also planned or in progress. Clearly we are only beginning to discover the impact capecitabine may have in the treatment of solid tumour patients.

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