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Capecitabine

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Contents

Abstract

▲ Capecitabine is an orally administered fluoropyrimidine carbamate used for the treatment of paclitaxel- or anthracycline-refractory breast cancer.

▲ Capecitabine is metabolised via a 3-step process to the active agent fluorouracil. The final step of this process occurs preferentially in malignant tissue.

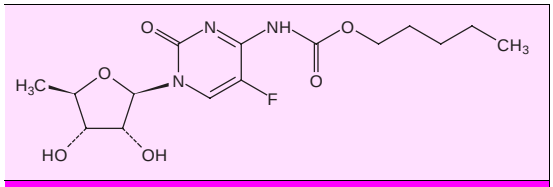
▲ In patients with paclitaxel-refractory breast cancer receiving capecitabine (2510 mg/m^2/day for 2 weeks of a 3-week cycle) the objective tumour response rate was 20%. Disease progression occurred in 34% of patients and 40% had stable disease.

▲ In this trial, the median duration of response was 241 days. Disease progression or death occurred in 83% of patients, and median time to progression was 93 days. Median survival time was 384 days.

▲ In previously untreated patients with breast cancer, the response rate was higher and time to disease progression was longer after oral capecitabine (2510 mg/m^2/day for 2 weeks of a 3-week cycle) than after intravenous cyclophosphamide, methotrexate and fluorouracil therapy.

▲ In clinical trials, generally gastrointestinal or haematological adverse events were reported most frequently. Other commonly reported events included hand-and-foot syndrome, fatigue, hyperbilirubinaemia, dermatitis and anorexia.

Features and properties of capecitabine (RO 091978)	
Indications	
Breast cancer	Launched
Mechanism of action	
Antineoplastic agent	A fluoropyrimidine carbamate which is converted preferentially in tumour tissue via a 3-step process to the active cytotoxic agent fluorouracil
Dosage and administration	
Usual dosage	2500 mg/m^2/day for 2 weeks of a 3-week cycle
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (500 to 3500 mg/m^2/day or 892 to 2510 mg/m^2 single dose)	
Peak plasma concentration after single dose	2.4 to 3.9 mg/L (capecitabine) 0.2 or 0.7 mg/L (fluorouracil)
Time to peak plasma concentration	1.5h (capecitabine) 2h (fluorouracil)
Area under the plasma concentration-time curve after single dose	5 or 6 mg/L • h (capecitabine) 0.3 to 1.3 mg/L • h (fluorouracil)
Elimination half-life	0.75h (capecitabine and fluorouracil)
Plasma protein binding	<60% (capecitabine and fluorouracil)
Adverse events	
Most frequent	Haematological: lymphopenia, anaemia, neutropenia, thrombocytopenia Gastrointestinal: diarrhoea, nausea, vomiting, stomatitis Others: hand-and-foot syndrome, fatigue, hyperbilirubinaemia, dermatitis, anorexia
Serious events	Haematological, gastrointestinal



Capecitabine

Capecitabine is an orally administered fluoropyrimidine carbamate approved for the treatment of metastatic breast cancer that is resistant to treatment with paclitaxel or anthracyclines or when anthracycline therapy is no longer indicated.[1]

Capecitabine is activated by a 3-step conversion process involving the enzymes carboxylesterase, cytidine deaminase and thymidine phosphorylase (TP), which are located in the liver and in tumours. The final step is the tumour-activated conversion to the cytotoxic agent fluorouracil by TP, found predominantly in malignant cells.[2,3] This site-specific action of capecitabine may potentially result in higher fluorouracil concentrations at the tumour site and, because of reduced systemic exposure to fluorouracil, lower toxicity than that associated with directly administering fluorouracil.[4] TP levels correlate with disease severity; thus capecitabine may be useful in high risk patients.[2]

1. Pharmacodynamic Profile

In Vitro Studies

- The location of enzymes involved in the activation of capecitabine was determined in an *in vitro* examination using various types of human tumour tissue and healthy tissue which were adjacent to these tumours.[5]

- The enzyme carboxylesterase was found predominantly in human liver and hepatoma cells, and enzyme activity was similar in these 2 tissue types. Cytidine deaminase was present in relatively high levels in many types of tumour and healthy tissue and was the highest in healthy liver tissue. The activity of TP was 3 to 10 times higher in all tumour tissue than in adjacent healthy tissue ($p < 0.05$), and higher in healthy tissue adjacent to the liver than in healthy tissue adjacent to other tumour types.[5]

- In the same study, using various human cancer cell lines, concentrations at which cell growth was inhibited by 50% compared with controls (IC_{50}) were higher for capecitabine (generally >1000 μmol/L) and the intermediary metabolites 5′-deoxy-5-fluorocytidine (generally >1000 μmol/L) and 5′-deoxy-5-fluorouridine (0.36 to 190 μmol/L) than for fluorouracil (0.25 to 21 μmol/L). Thus, fluorouracil was stated to have the greatest cytotoxic activity.[5]

- In another *in vitro* examination of antiproliferative activity, the IC_{50} was also higher with capecitabine than with fluorouracil (185 *vs* 0.85 μmol/L).[6]

Animal Studies

- In murine xenograft models inoculated with various human cancer cell lines, the antitumour activity of oral capecitabine (2.1 or 1.5 mmol/kg/day for 5 or 7 days per week, respectively, for 2 to 4 weeks) correlated with tumour TP levels ($p = 0.016$) but not with levels of dihydropyrimidine dehydrogenase (DPD; involved in the inactivation of fluorouracil). Furthermore, the efficacy of capecitabine correlated with the ratio of TP to DPD in tumour tissue ($p = 0.0015$).[7]

- The antitumour efficacy, but not the toxicity, of oral capecitabine (maximum tolerated dose administered 5 times a week) was increased by the addition of intravenous paclitaxel (15 mg/kg) or docetaxel (100 mg/kg) in murine models inoculated with human colon or breast cancer cells. This tumour regression effect was more than additive and possibly synergistic.[8]

- In contrast, the effect on tumour regression was only additive when paclitaxel was coadministered with intraperitoneal fluorouracil. The enhanced efficacy of capecitabine may be explained by the significant increase in tumour cell TP and tumour necrosis factor levels observed with paclitaxel and docetaxel. The increased tumour cell TP level does not appear to influence the efficacy of fluorouracil which, unlike capecitabine, does not rely on TP to modulate its effect.[8]

• In a study comparing the tumour selectivity of capecitabine (oral, 2.1 or 1.5 mmol/kg/day for 5 or 7 days per week for 3 or 4 weeks) and fluorouracil (oral or intraperitoneal, 0.21 or 0.15 mmol/kg/day for 5 or 7 days per week for 3 or 4 weeks), murine models were inoculated with 4 human colon cancer cell lines, 1 of which was refractory to both drugs.[9]

• Capecitabine inhibited tumour growth by more than 50% in all but the refractory cell line model. Furthermore, after capecitabine, tumour site fluorouracil concentrations were greater than those in plasma (by about 37 to 209 times) and in muscle (by about 22 times).[9]

• In contrast, fluorouracil inhibited tumour growth in only 1 cancer cell line model which was particularly susceptible to these agents, and in general fluorouracil concentrations at the tumour site were similar to those in muscle and plasma. In addition, tumour site concentrations of fluorouracil were higher after capecitabine than after fluorouracil (16- to 35-fold in the 3 susceptible cancer models and 5.5-fold in the refractory model).[9]

• The therapeutic index of capecitabine (twice daily for 2 to 4 weeks; dose not specified) in mice inoculated with 12 human cancer cell lines ranged from 1.5 to >40 and was greater than that of oral fluorouracil administered by the same dose regimen (therapeutic index = 2 for a human colon cancer model).[6]

• In the same study, in mice inoculated with metastatic murine tumour cells, capecitabine was selective for metastases rather than for the primary tumour; the lowest dose at which tumour growth was inhibited by more than 50% (minimum effective dose) was 64-fold greater for the primary tumour. In contrast, the minimum effective dose of fluorouracil was only 4-fold greater for the primary tumour than for metastases.[6]

Studies in Patients

• The maximum tolerated dose (MTD) and the maximum acceptable dose (MAD) of oral capecitabine administered twice daily either continuously or intermittently were determined in groups of 6 to 34 patients with various types of solid tumours.[10-12] In these nonblind studies most patients had received previous treatment with conventional therapy. However, results from previously treated and untreated patients were not reported separately.

• Using the National Cancer Institute common toxicity criteria, the MTD was defined as the dose causing drug-related toxicities of grade 3 (severe) or 4 (life threatening) severity in one-third or more of patients.[10-12] The MAD was defined as the dose at which 4 or more patients experienced ≥ grade 2 toxicity (moderate) requiring interruption of treatment for more than 14 days.[10]

• In one study, the MTD of capecitabine (110 to 2083 mg/m^2/day continuously for at least 6 weeks) was 1657 mg/m^2/day, and grade 3 or 4 toxicities occurred only at this dose. The MAD was 1331 mg/m^2/day.[10]

• In a study in which capecitabine was administered intermittently (502 to 3514 mg/m^2/day for 2 weeks of each 3-weekly cycle for a median of 4 cycles), the MTD was 3000 mg/m^2/day and the MAD was 2510 mg/m^2/day.[11]

• In another study, in which oral folinic acid (60 mg/day) was given concomitantly with capecitabine, the MTD of continuously administered capecitabine (1004 mg/m^2/day, which was to be the starting dose, for 3 to 17 weeks) was 1004 mg/m^2/day, and 2000 mg/m^2/day when administered intermittently (1004 to 2510 mg/m^2/day for 2 weeks of each 3-weekly cycle for 1 to 41 weeks). The MAD of intermittently administered capecitabine in combination with folinic acid was 1650 mg/m^2/day.[12]

• The tumour selectivity of capecitabine has been shown in a study, presented as an abstract, in 19 patients with colorectal cancer and liver metastasis receiving oral capecitabine 1255 mg/m^2 twice daily for 5 to 7 days. Compared with that in healthy tissue, the concentration of fluorouracil in the primary tumour was about 3.2 times greater but the concentration in metastatic liver tissue was similar.[13]

• The difference in tumour selectivity between colorectal tissue and the liver may be explained by the higher levels of TP and cytidine deaminase

(involved in the activation of capecitabine) in the colorectal area compared with healthy tissue (4.1 and 3.4 times greater, respectively). Enzyme activities in the liver were similar to those observed in healthy tissue.[13]

2. Pharmacokinetic Profile

Data on the pharmacokinetic parameters of capecitabine and fluorouracil have been obtained from the manufacturer's prescribing information[1] and from studies in 6 to 10 patients with solid tumours that were refractory to other treatments.[10-12] In 1 trial patients received concomitant oral folinic acid (60 mg/day).[12]

- After oral administration of capecitabine (500 to 3500 mg/m^2/day) to 200 patients with cancer, pharmacokinetic parameters showed a linear dose response. In general, duration of administration did not affect these parameters, although the area under the plasma-concentration time curve (AUC) of fluorouracil and another metabolite, 5′-deoxy-5-fluorouridine, increased disproportionately to the increase in dose. Furthermore, the AUC of fluorouracil was 34% higher on day 14 than on day 1.[1]

- After single dose oral capecitabine (892 to 2510 mg/m^2) taken within 30 minutes of the end of a meal, the mean maximum plasma concentration (C_{max}) ranged from about 2.4 to 3.9 mg/L, and the mean $AUC_{0-\infty}$ was about 5 or 6 mg/L · h. Corresponding values for fluorouracil were about 0.2 or 0.7 mg/L and about 0.3 to 1.3 mg/L · h.[10-12] Large variation between patients is observed in C_{max} and AUC values of fluorouracil.[1]

- C_{max} for capecitabine is reached in 1.5 hours and 2 hours for fluorouracil. Less than 60% of capecitabine and its metabolites are bound to plasma protein. The elimination half-life ($t_{1/2}$) of both capecitabine and fluorouracil is about 0.75 hours, and more than 70% of the administered dose is recovered in the urine.[1]

- Capecitabine is metabolised in the liver to 5′-deoxy-5-fluorocytidine by the enzyme carboxylesterase, and then to 5′-deoxy-5-fluorouridine by cytidine deaminase which is found in most tissues including tumours. The final step is conversion to fluorouracil by TP which is present in higher levels in malignant, than in healthy, tissue.[1]

- The presence of food reduced the rate and extent of absorption of capecitabine and fluorouracil. The C_{max} and $AUC_{0-\infty}$ of capecitabine were reduced by 60 and 35%, respectively; corresponding parameters for fluorouracil decreased by 43 and 21% when the drug was administered immediately after food compared with values in fasting patients. The t_{max} of both agents increased by 1.5 hours.[1]

- In 13 patients with mild to moderate hepatic dysfunction caused by liver metastases, who received single dose oral capecitabine (1255 mg/m^2), C_{max} and $AUC_{0-\infty}$ of this drug increased by 60% compared with patients with normal hepatic function but corresponding values for fluorouracil were not affected. The effects of severe hepatic or renal dysfunction on capecitabine and fluorouracil pharmacokinetics have not yet been determined.[1]

- According to *in vitro* studies, pharmacokinetic interactions between capecitabine and drugs metabolised by the cytochrome P450 enzymes are unlikely. Drug interactions involving plasma protein binding are also predicted to be rare.[1] In 31 patients with metastatic cancer the concomitant administration of folinic acid with capecitabine did not significantly alter capecitabine pharmacokinetics.[12]

- The administration of 20ml of an antacid containing aluminium hydroxide and magnesium hydroxide immediately after capecitabine (1250 mg/m^2) increased the AUC and C_{max} of capecitabine (by 16 and 35%, respectively) and of the metabolite 5′-deoxy-5-fluorocytidine (by 18 and 22%), but not of fluorouracil, in 12 patients with cancer.[1]

3. Therapeutic Trials

In Previously Treated Patients

- A phase II multicentre, nonblind, noncomparative trial was conducted in 162 patients with paclitaxel-refractory metastatic breast cancer, most

of whom had also received previous anthracyclines (91%).[14]

• Patients received oral capecitabine 2510 mg/m^2/day in 2 divided doses for 2 weeks of each 3-week cycle, adjusted if adverse events developed. Duration of treatment was dependent on disease progression: treatment was given for at least 43 days and continued for 18 weeks (treatment) or 48 weeks (maintenance) in patients with objective responses or stable disease. Patients with no disease progression at 48 weeks could continue treatment until progression was apparent.[14]

• The primary end-point was an objective response rate of 20% (complete plus partial response). A complete response was defined as the disappearance of all disease, a partial response as a 50% reduction in the size of all tumours, progressive disease as an increase in size of any tumour by 25% or the development of new tumours, and stable disease as all other outcomes.[14]

• Additional end-points included duration of response, time to disease progression, survival and assessments of clinical benefit which included patients' pain intensity, analgesic consumption and the Karnofsky performance status. The results of the trial were based on an intention-to-treat analysis. A statistical analysis was not reported for any result in this trial.[14]

• 135 patients had measurable disease, and of these 2.2% showed a complete response, 17.8% showed a partial response, 40% had stable disease and 34% showed disease progression within the first 6 weeks of treatment (fig. 1). Responses were observed in all metastatic sites. Responders to capecitabine (n = 27) showed a reduction in tumour size by a mean of 81%, and the median duration of response in these patients was 241 days. However, in 11 patients with a response, disease progression was still not apparent at the end of the observation period.[14]

• In a retrospectively identified subgroup of 42 of these patients who were resistant to both paclitaxel and doxorubicin, the response rate was 29%.[14]

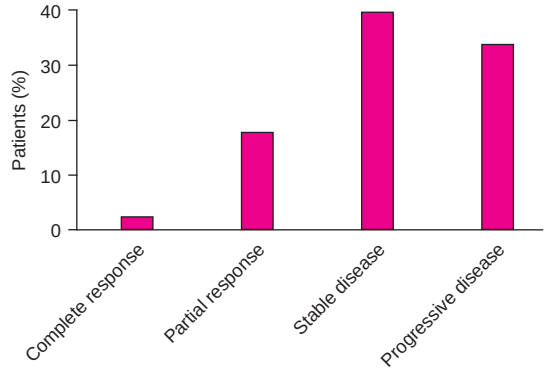


Fig. 1. Tumour response rates to oral capecitabine in patients with metastatic breast cancer. Response rates to treatment with oral capecitabine (2510 mg/m^2/day for 2 weeks of a 3-week cycle) in 135 patients with paclitaxel-refractory metastatic breast cancer.[14]

• In 27 patients with assessable, but not measurable, disease, 19% showed a complete or partial response for a duration of 161 to more than 235 days.[14]

• When results from all 162 patients were combined, disease progression or death occurred in about 83% of patients, and the median time to disease progression was 93 days. The median survival time was 384 days.[14]

• The overall clinical benefit response to capecitabine was assessed in 147 patients and was positive in 20% of patients (improvement in at least 1 parameter and at least stable in the other 2), stable in 30% of patients (all 3 parameters unchanged) and negative in 50% of patients (deterioration in any parameter).[14]

• A comparative trial, presented as an abstract, was conducted in 44 patients with previously treated breast cancer who were resistant to prior anthracycline therapy.[15] A between-treatment statistical analysis was not reported.

• In this trial the response rate to oral capecitabine (2510 mg/m^2/day in 2 doses for 2 weeks of a 3-week cycle) was higher than that to paclitaxel (175 mg/m^2 on day 1 every 3 weeks) [36 *vs* 21%]. The

median time to disease progression was similar to that with paclitaxel (92 *vs* 95 days).[15]

As First-Line Therapy

- In a comparative trial, presented as an abstract, 93 previously untreated patients with breast cancer received oral capecitabine (2510 mg/m^2/day in 2 doses for 2 weeks of a 3-week cycle). The response rate to capecitabine was higher than that to combination therapy with intravenous cyclophosphamide, methotrexate and fluorouracil (CMF; administered on day 1 every 3 weeks) [25 *vs* 16%]. The median time to disease progression was longer with cape-

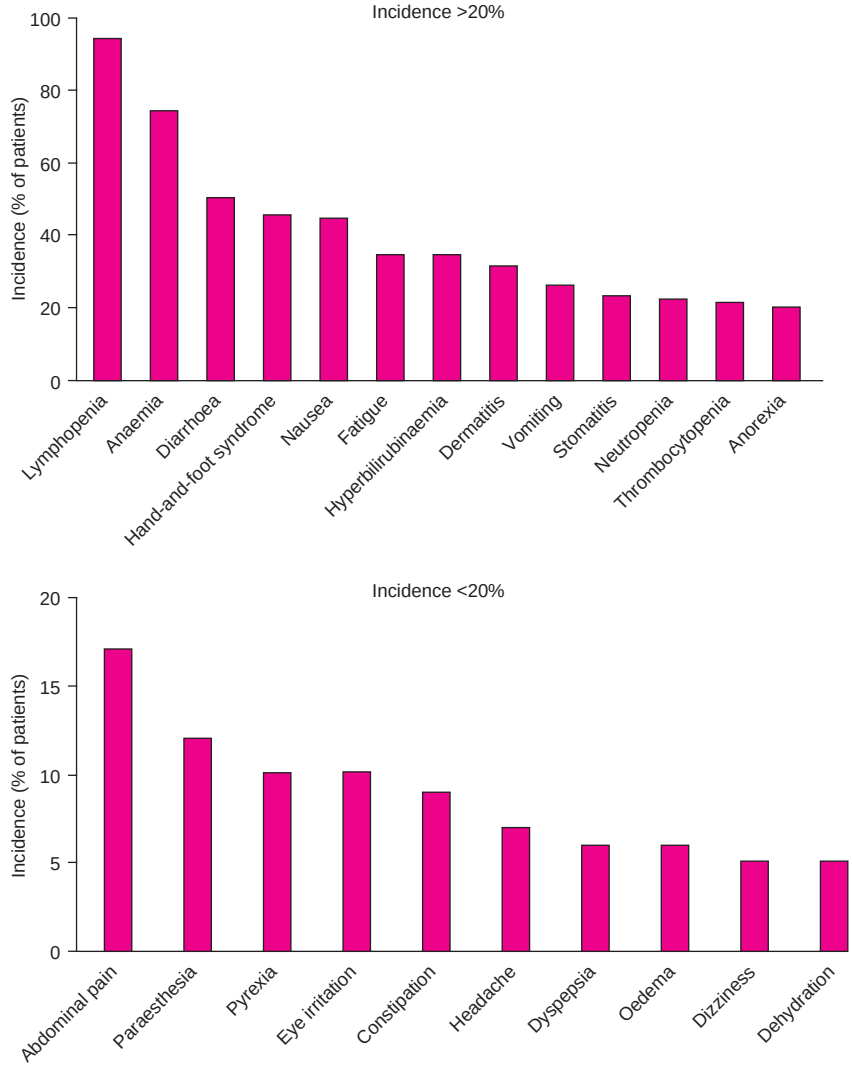


Fig. 2. Incidence of adverse events after oral capecitabine. Adverse events with an incidence of ≥5% reported after oral capecitabine (2510 mg/m^2/day for 2 weeks of a 3-week cycle) by 570 patients with breast or colorectal cancer.[1]

citabine than with CMF (132 *vs* 94 days).[16] A between-treatment statistical analysis was not reported.

4. Tolerability

Data presented in this section have been obtained from the manufacturer's prescribing information.[1] This provides the incidence of adverse events reported in clinical trials by 570 patients with breast or colorectal cancer receiving capecitabine 2510 mg/m^2/day for 2 weeks of a 3-weekly cycle. These patients include the 162 patients with metastatic breast cancer from the clinical trial presented in section 3. Additional information from this clinical trial has also been included in this section (see section 3 for study details).[14] These trials used the National Cancer Institute of Canada common toxicity criteria (version 1) to grade the severity of adverse events (W. Behrens and S. Frings, personal communication).

- The most frequently reported adverse events after capecitabine were generally haematological (incidence of 21 to 94%) or related to the gastrointestinal system (incidence of 6 to 50%). In addition, hand-and-foot syndrome (painful erythema and swelling) [45%], fatigue (34%), hyperbilirubinaemia (34%), dermatitis (31%) and anorexia (20%) were also commonly reported (fig. 2).[1]

- In general, the incidence of events which were of grade 3 or 4 severity was relatively low (1 to 14% and 1 to 10%, respectively); however, grade 3 lymphopenia was reported by 36% of patients. Other frequently reported grade 3 events included hyperbilirubinaemia (1.5 to 3 times the normal level) [14%], hand-and-foot syndrome (13%) and diarrhoea (11%). Grade 4 lymphopenia occurred in 10% of patients. 13% of patients discontinued treatment because of adverse events or intercurrent illness.[1]

- In the clinical trial in patients with metastatic breast cancer, the most commonly reported adverse events were hand-and-foot syndrome (56.2%), diarrhoea (54.3%), nausea (51.9%), vomiting (37%) and fatigue (36.4%). Overall most of these events were of mild or moderate intensity. Significant hair loss did not occur with capecitabine use. The events leading most commonly to withdrawal from the study were abdominal pain or diarrhoea, with each event resulting in the withdrawal of 2% of patients. No drug-related deaths were noted.[14]

- In this trial, elevated total plasma bilirubin levels was the most commonly reported change in laboratory parameters and was of grade 3 or 4 severity (1.5 to >3 times the normal level[1]) in 10.5% (n = 17) of patients. However, in 9 of these patients this change corresponded with progressive metastatic liver disease. Other laboratory parameters worsened to grade 3 or 4 severity in 0 to 4.3% of patients.[14]

5. Capecitabine: Current Status

Capecitabine is an orally active antineoplastic agent approved in some countries for the treatment of metastatic breast cancer which is resistant to paclitaxel and anthracycline or in patients in whom anthracyclines are no longer indicated. This drug is also undergoing clinical trials worldwide for the treatment of colorectal and gastric cancer. Capecitabine has shown clinical efficacy in patients with paclitaxel-refractory metastatic breast cancer in 1 trial. In general, adverse events associated with capecitabine were of mild to moderate intensity. The most common events were of a haematological or gastrointestinal nature, but hand-and-foot syndrome, fatigue, hyperbilirubinaemia, dermatitis and anorexia were also frequently reported.

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