A Phase I Study of Capecitabine in Combination with Oral Leucovorin in Patients with Intractable Solid Tumors

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ABSTRACT
Capecitabine (Xeloda™) is a novel rationally designed fluoropyrimidine carbamate. It passes through the intestinal mucosal intact and is subsequently activated by a cascade of three enzymes resulting in preferential release of 5-fluorouracil (5-FU) at the tumor site. Preclinical studies indicated an enhancement of the therapeutic index when capecitabine was combined with leucovorin. This Phase I trial was designed to determine the safety profile, maximal tolerated dose, and pharmacokinetic profile of the combination of capecitabine plus a fixed dose of p.o. leucovorin (60 mg/day) during administration to patients with refractory advanced cancers. The intention was to administer both drugs continuously, but the starting dose of capecitabine was also the maximum tolerated dose (1004 mg/m²/day) in six patients treated with this regimen. A cycle of treatment was then redefined as leucovorin and capecitabine given p.o., twice daily for 2 consecutive weeks followed by a 1-week rest period. Capecitabine doses from 1004 mg/m²/day to 2510 mg/m²/day were evaluated with the intermittent schedule over approximately 80 courses in an additional 25 patients. The dose-limiting toxicities that defined the maximum tolerated dose at 2000 mg/m²/day were diarrhea, nausea, vomiting, and palmar plantar erythrodysesthesia. The recommended Phase II dose using this schedule was 1650 mg/m²/day of capecitabine plus leucovorin 60 mg/day. Plasma concentrations of capecitabine, intermediate metabolites, and 5-FU were measured in 26 patients on days 1 and 14 of therapy. The pharmacokinetics of capecitabine were characterized by rapid GI absorption, with Cmax at 1 h, followed by conversion to active drug. The coadministration of leucovorin had no effect on the pharmacokinetics of capecitabine. Two patients with colorectal cancer, both previously treated with 5-FU, had partial responses. Phase II studies have confirmed the promising antitumor activity of this drug, and capecitabine is currently in Phase III evaluation.

INTRODUCTION
5-FU³ has been the mainstay of chemotherapeutic management of GI malignancies for 30 years. In that time, many derivative compounds have been evaluated, but none has surpassed the clinical utility of the parent. Capecitabine (Xeloda™) is a novel fluoropyrimidine carbamate (Fig. 1) that was rationally designed to be absorbed intact from the GI tract and then metabolically activated to 5-FU selectively in tumors. After p.o. administration, capecitabine passes through the intestinal mucosa into the portal circulation as the intact molecule. Capecitabine is metabolized in the liver to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumor tissue. Further catalytic activation of 5'-DFUR to 5-FU then occurs within the tumor by the tumor-associated angiogenic factor thymidine phosphorylase (also known as PD-EGF) which is preferentially expressed in tumor (1). This results in prolonged exposure of 5'-DFUR as well as the targeting of tumor cells because of the principle location of cytidine deaminase and PyNPase. Capecitabine was shown to be highly active in preclinical xenograft models in a variety of solid tumor types, including 5-FU-resistant tumors (1-5).

The therapeutic advantage of continuous infusion 5-FU over bolus administration (6, 7) is hampered by the inconvenience and complications of central venous access (8). Delivery of capecitabine by continuous p.o. administration may obviate these difficulties. Leucovorin modulates the inhibition of thymidylate synthase by 5-FU by stabilization of the quaternary complex formed by the binding of fluoro-dUMP to thymidylate synthase. Preclinical studies demonstrated an improvement of activity without worsening of toxicity when leucovorin was coadministered with capecitabine (4). It was, therefore, decided to initiate a human Phase I study with this combination regimen. In parallel, Phase I studies were conducted with single-agent intermittent and continuously administered capecitabine (9, 10). The intention in this study was to explore continuous administration of capecitabine with leucovorin, but this resulted in insufficient toxicity to define the MTD at the starting dose. The study schedule was, therefore, modified to 2 weeks of drug administration followed by 1 week of rest, with 3 weeks constituting one cycle of therapy.

1 The abbreviations used are: 5-FU, 5-fluorouracil; GI, gastrointestinal; 5'-DFCR, 5'-deoxy-fluorocytidine; 5'-DFUR, 5'-deoxy-5-fluorouridine; MTD, maximum tolerated dose; PPE, palmar plantar erythrodysesthesia; NCIC-CTC, National Cancer Institute of Canada-Common Toxicity Criteria; AUC, area under the curve; CV, coefficient of variation; FUH², dihydro-5-fluorouracil; FBAL, α-fluoro-β-alanine.
Capecitabine Phase I

**Fig. 1** Capecitabine (Xeloda™) is absorbed intact from the GI tract and then metabolically activated to 5-FU.

Preclinical toxicology studies of capecitabine were conducted in mice, rats, and cynomolgus monkeys, the latter chosen because of the similar substrate specificities of hepatic and intestinal acylamidases compared with man. Briefly, the toxicity profile in all of the species was similar to 5-FU, with diarrhea and leukopenia. In monkeys, the highest nontoxic dose levels with continuous p.o. administration of capecitabine for 4 and 13 weeks were 35.9 and 54 mg/kg/day, respectively (11). The starting dose for this human Phase I study was guided by preliminary clinical experience with continuous single-agent capecitabine and was 1004 mg/m²/day (9, 10). Because there was little information on both acute and chronic toxicity of capecitabine in humans, a novel overlapping-dose escalation scheme was devised and implemented in this study.

A low-dose p.o. leucovorin modulation was included in this Phase I study. The dose of 60 mg/day was selected after two publications in colorectal cancer that showed no difference in objective response rate for low-dose (20 mg/m²/day) versus high-dose (200 mg/m²/day) leucovorin combined with 5-FU given for 5 consecutive days per month (12, 13). The effectiveness of low-dose leucovorin was confirmed in a subsequent clinical trial (14). Although these trials used the i.v. route, the active isomer of leucovorin has been shown to be completely bioavailable for p.o. doses up to 40 mg with a selective uptake of the active isomer. Absorption is, however, saturable at doses of 50 and 100 mg (15). This information together with the potentiation of both 5-FU and doxifluridine by p.o. leucovorin and the obvious advantage of a completely p.o. combination using identical schedules provides the logical rationale for the selection of this dose and schedule of p.o. leucovorin.

**PATIENTS AND METHODS**

This was an open label, two-center, Phase I study to determine the MTD and to evaluate the safety, tolerance, and pharmacokinetics of twice daily p.o. administration of capecitabine when combined with p.o. leucovorin. All of the patients gave written informed consent to the study before entry, and the study was reviewed and approved by the local Ethics Review Board. The study was conducted to Good Clinical Practice guidelines and monitored by Hoffmann-La Roche and Quintiles personnel.

**Patient Selection.** Patients with histologically confirmed metastatic cancer refractory to conventional treatment were entered into the study after fully informed written consent had been obtained. Specific eligibility criteria included: (a) age ≥18 years; (b) Karnofsky performance status of ≥70%; life expectancy of at least 3 months; and (c) ability to comply with protocol and follow-up requirements. Specific exclusion criteria were: (a) pregnant or lactating females; (b) failure to use reliable contraception for the duration of the study; (c) previous organ allograft; (d) clinically significant cardiac disease (defined by New York Heart Association, class III or IV); (e) brain metastases; (f) impaired renal function (serum creatinine ≥180 μmol/liter); (g) hyperuricemia or hypercalcemia (urate ≥0.52 mmol/liter, calcium ≥2.88 mmol/liter); (h) impaired hepatic function (bilirubin ≥33 μmol/liter, transaminases or alkaline phosphatase >2.5 × the upper limit of normal); (i) previous chemotherapy or radiotherapy within 4 weeks of the start of treatment (6 weeks for nitrosoureas, mitomycin C, or melphalan); (j) major surgery in the preceding 4 weeks that could impact on drug absorption, metabolism, or excretion; and (k) other serious uncontrolled intercurrent illness.

A total of 31 patients were entered into the study; their characteristics are summarized in Table 1. Pretreatment evaluation involved: (a) a complete physical examination; (b) ECG; (c) chest radiograph; (d) urinalysis, and (e) the measurement of standard hematological and biochemical parameters. In addition, measurements of evaluable disease were made by appropriate radiological imaging. Patients attended weekly for 6 weeks, then every 2–3 weeks for treatment, monitoring of adverse events (using NCIC-CTC criteria), physical examination, and repeat estimations of hematological and biochemical parameters. PPE was graded: (a) mild (grade 1, asymptomatic reddening of the palms of the hands and/or soles of the feet); (b) moderate (grade 2, exfoliation of the skin and/or some discomfort but no loss of function), and (c) severe (grade 3, fissuring of the skin and/or functional impairment). Evaluation of tumor response was performed every 6 weeks by appropriate clinical and radiological assessment.

**Drug Administration.** Capecitabine was supplied as film-coated tablets at four dose strengths: 100 mg, 150 mg, 500 mg, and 750 mg. The tablets were packed in Triplex blister packing strips of seven tablets, with strengths of different tablets identified by color-coded cards. Capecitabine was taken p.o., as two equally divided doses given 12 h apart, within 30 min of the end of a meal. In addition, all of the patients were to receive p.o. leucovorin (30-mg/dose) twice daily, to be taken at the same time as the capecitabine dose. Compliance with medication was assessed by tablet counts at each clinic visit.

The starting dose of capecitabine was selected as the highest drug dose fully explored in the ongoing continuous twice daily p.o. single-agent Phase I study (9) for which no grade 3 adverse events had been noted. The available clinical data at that time suggested a safe starting dose of 1004 mg/m²/day, given in
two divided doses with leucovorin. This approach was adopted to minimize the number of patients treated at potentially subtherapeutic levels. A modified Fibonacci scheme of dose escalation that paralleled the ongoing single-agent Phase I studies was planned (9, 10). If, after a minimum of 3 weeks of treatment in three patients and 6 weeks in at least one patient, drug-related toxicity did not exceed grade 1 in any patient, the decision was made to escalate dosage for the next cohort of patients. This staggered entry and follow-up scheme allowed experience in all of the cohorts with varied duration of therapy to be simultaneously evaluated to assess both acute and chronic toxicities. The study was designed to expose all of the patients to a combination of capecitabine plus leucovorin for at least 6 weeks. Patients with good tolerance of therapy and stable or responding disease were allowed to continue therapy beyond this time point until disease progression.

The following guidelines were applied for dose modifications for toxicity. For any grade 1 toxicity, treatment continued without modification. In the event the grade 2 toxicity that did not resolve with suitable symptomatic therapy, then drug administration was withheld until resolution to grade 0–1 at which time, treatment was restarted at the same dose with prophylactic therapy where necessary. If the same grade 2 toxicity recurred, treatment was stopped until resolution and then restarted at the previous dose level. If grade 3 toxicity was observed, drug administration was withheld until resolution to grade 0–1 and then restarted at the preceding dose level. In the event of any grade 4 toxicity, treatment could only be restarted if the investigator felt this to be in the patient’s best interest. After any dose reduction, this dose was then maintained with no re-escalation of doses in subsequent cycles.

The first six patients were treated with capecitabine plus leucovorin using a continuous dosing regimen. The starting dose with this regimen (1004 mg/m²/day capecitabine) proved to be the MTD, and the study protocol was amended to allow for an intermittent dosing schedule, with a 3-week cycle comprising 2 weeks of treatment and 1 week of rest. The MTD was then defined as the twice daily p.o. dose of capecitabine which, given over a 6-week period as two cycles of intermittent therapy in combination with leucovorin (60 mg/day), caused NCIC-CTC grade 3 or 4 toxicity in one-third or more of the patients treated.

**Clinical Pharmacological Studies.** Blood sampling was performed in all of the patients for the estimation of plasma concentrations of capecitabine and its metabolites. To define any potential pharmacokinetic interactions between capecitabine and leucovorin, each patient had serial blood samples taken on both days 1 and 14 of the first cycle of therapy. On the 1st day, leucovorin was omitted but was taken with capecitabine on day 14. Thus, each patient served as his/her own control for comparisons of with- and without-leucovorin capecitabine pharmacokinetic parameters. Serial blood samples were obtained from a single indwelling cannula before capecitabine administration and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h after capecitabine administration on both days. Samples were collected into glass heparinized tubes and centrifuged. The plasma was transferred into a plain plastic tube on day 1, but on day 14, heparinized plasma was transferred into a plastic tube containing ascorbic acid as an antioxidant. Plasma samples were stored at −20°C until analysis.

**Drug Analysis.** Concentrations of capcitabine and its metabolites 5'-DFCR, 5'-DFUR, 5-FU, FUH₂, and FBAL were measured using a validated liquid chromatography mass spectrometry technique and a high-performance liquid chromatography-UV technique as described previously (15).

Plasma concentrations of leucovorin and 5-methyltetrahydrofolic acid were measured using a validated, specific high-performance liquid chromatography-MS/MS method at Hoffmann-La Roche Inc. (Nutley, NJ). Folic acid and 5-methyltetrahydrofolic acid were extracted from plasma using solid phase extraction. The extracts were applied to a Waters Nova-Pak C-18 (4 μm), 3.9 × 150-mm column and quantified by mass spectrometry. Samples were assayed according to in-house standard operating procedures and Good Laboratory Practice standards. Interassay and intra-assay CVs were less than 10%.

**Pharmacokinetic Calculations.** Estimation of the pharmacokinetic parameters of capecitabine and its metabolites was performed according to standard noncompartmental methods (6). The Cmax and tmax were taken from the observed data; t1/2 was estimated from ln(2)/k, where the apparent rate constant of elimination (k) was estimated by linear regression on the logarithm of the plasma concentration versus time data; area under the concentration time curve from time 0 to infinity was estimated from the sum of AUC₀–₄ and Cₘₚ/k. AUC₀–₄ was estimated using the linear trapezoidal method.

The effect of leucovorin on the pharmacokinetics of capecitabine and its metabolites were investigated by comparing the results without leucovorin (day 1) and with leucovorin (day 14).

**RESULTS**

Fifteen female and 16 male patients (ages 42–76 years; mean, 59.4) were enrolled. All of the patients were Caucasians with Karnofsky Performance status between 70 and 100%.

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**Table 1 Dosing groups**

<table>
<thead>
<tr>
<th>Capecitabine (mg/m²/day)</th>
<th>Patients, n</th>
<th>Age (yr. median)</th>
<th>Male/Female</th>
<th>Prior chemotherapy</th>
<th>Mean no. of cycles given</th>
<th>Wk on study</th>
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</thead>
<tbody>
<tr>
<td>1004 (cont)²</td>
<td>6</td>
<td>64.3</td>
<td>4/2</td>
<td>4</td>
<td>3.3</td>
<td>3–17</td>
</tr>
<tr>
<td>1004 (int)</td>
<td>6</td>
<td>54.5</td>
<td>2/4</td>
<td>6</td>
<td>4.2</td>
<td>6–41</td>
</tr>
<tr>
<td>1657</td>
<td>6</td>
<td>57.7</td>
<td>2/4</td>
<td>4</td>
<td>3.0</td>
<td>1–19</td>
</tr>
<tr>
<td>2000</td>
<td>7</td>
<td>65.3</td>
<td>4/3</td>
<td>4</td>
<td>3.2</td>
<td>2–11</td>
</tr>
<tr>
<td>2510</td>
<td>6</td>
<td>54.6</td>
<td>4/2</td>
<td>3</td>
<td>2.5</td>
<td>2–12</td>
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</table>

² cont, continuous; int, intermittent.
Table 2  Hematological toxicity (NCIC-CTC)

<table>
<thead>
<tr>
<th>Dose level (no. of patients)</th>
<th>Hemoglobin</th>
<th>Platelets</th>
<th>Leukocytes</th>
<th>Granulocytes</th>
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<td>0 1 2 3 4</td>
<td>0 1 2 3 4</td>
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<td>1004c(6)</td>
<td>0 4 2 0 0</td>
<td>0 0 0 0 0</td>
<td>5 1 0 0 0</td>
<td>6 0 0 0 0</td>
</tr>
<tr>
<td>1004i(6)</td>
<td>1 2 3 0 0</td>
<td>0 6 0 0 0</td>
<td>5 0 0 1 0</td>
<td>5 1 0 0 0</td>
</tr>
<tr>
<td>1657(6)</td>
<td>0 2 4 0 0</td>
<td>0 6 0 0 0</td>
<td>5 1 0 0 0</td>
<td>5 1 0 0 0</td>
</tr>
<tr>
<td>2000(7)</td>
<td>0 4 3 0 0</td>
<td>0 4 3 0 0</td>
<td>4 1 1 1 0</td>
<td>5 1 0 1 0</td>
</tr>
<tr>
<td>2510(6)</td>
<td>0 5 1 0 0</td>
<td>0 5 1 0 0</td>
<td>6 0 0 0 0</td>
<td>6 0 0 0 0</td>
</tr>
</tbody>
</table>

a, continuous; i, intermittent.

Table 3  Nonhematological adverse events (NCIC-CTC)* (Part 1)

<table>
<thead>
<tr>
<th>Dose level (no. of patients)</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Stomatitis</th>
<th>Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1 2 3 4</td>
<td>1 2 3 4</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>1004c(6)</td>
<td>2 0 1 0</td>
<td>2 1 0 1</td>
<td>1 3 1 0</td>
<td>1 0 1 0 0</td>
<td>0 1 0 0 0</td>
</tr>
<tr>
<td>1004i(6)</td>
<td>3 0 0 0</td>
<td>0 1 0 2</td>
<td>0 0 0 0</td>
<td>0 0 0 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>1657(6)</td>
<td>3 1 0 0</td>
<td>1 1 0 0</td>
<td>0 2 1 0</td>
<td>1 0 1 0 1</td>
<td>0 1 0 0 0</td>
</tr>
<tr>
<td>2000(7)</td>
<td>4 1 0 0</td>
<td>3 1 0 3</td>
<td>2 1 0 1</td>
<td>0 1 1 0 0</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>2510(6)</td>
<td>2 0 1 0</td>
<td>2 0 1 0</td>
<td>3 1 0 1</td>
<td>1 0 3 1 0</td>
<td>0 1 0 0 0</td>
</tr>
</tbody>
</table>

a Number of patients experiencing toxicity at maximum grade per patient at each dose level within the first 42 days of treatment.

b c, continuous; i, intermittent.

dose- and schedule-dependent with capecitabine and leucovorin and were more frequent in the continuous-treatment group and in the higher-dose intermittent-treatment groups.

Adverse Events in Patients with Capecitabine plus Leucovorin. A total of 229 clinical adverse events were reported by the 31 patients in this study. Of these, 126 were judged by the investigators as drug-related. Among all of the events, 56% were mild (grade 1), 33% were moderate (grade 2), and 11% were severe (grade 3). Of these life-threatening events were in the same patient, and both were considered unrelated to treatment. There were no treatment-related deaths. No routine prophylactic treatment to prevent adverse events was given. A summary of the major hematological and clinical adverse events observed for each dose level is presented in Tables 2–5.

The most commonly reported drug-related adverse events were diarrhea, nausea, vomiting, stomatitis, and PPE (or hand-foot syndrome). These were very similar to the well-known adverse events experienced by patients treated with continuous infusion 5-Hi (6, 7). These side-effects appeared to be both dose- and schedule-dependent with capecitabine and leucovorin and were more frequent in the continuous-treatment group and in the higher-dose intermittent-treatment groups.

The first cohort of 6 patients was treated at the dose level of capecitabine 1004 mg/m²/day (continuous schedule). Three patients at this dose level suffered from grade 3 adverse events (nausea, vomiting, and diarrhea). Because the criteria for MTD had been met by this continuous schedule, the protocol was amended to switch to an intermittent dosage schedule (cycles of 2 weeks of treatment followed by a 1-week treatment-free rest period; Ref. 10). At the (intermittent) dose level of 2510 mg/m²/day, three of six patients suffered grade 3 treatment-related adverse events. One had grade 3 nausea and vomiting, one had diarrhea, and one had hand-foot syndrome. This dose level was, therefore, considered at or above the MTD as defined in the
The recommended dose for Phase II evaluation was, therefore, 5).
ring in the first six weeks and is therefore not shown in Table
raised transaminases and attributable to biliary infection second-
bilirubin was normal. In one patient, this was associated with
completely during the 1-week treatment-free intervals.

Therapeutic Responses. A total of three patients
showed evidence of antitumor efficacy during this Phase I stidy:
(a) a 72-year-old male with previously treated lung and liver
metastases from a colon carcinoma. The patient’s best response
to previous therapy had been stable disease. He had a confirmed
partial response at day 127; and (c) a patient with previously
treated metastatic colorectal carcinoma who showed a signifi-
cant volume reduction of >25% but <50% in liver metastasis at
day 92 of therapy on a dose of 1657 mg/m²/day. An additional
16 patients had a best response of stable disease after receiving
1–5 months of treatment.

Pharmacokinetic Studies. A total of twenty-two pa-
tients are evaluable for pharmacokinetic analysis on both days 1
and 14. Table 6 shows summaries of statistics for capecitabine
and its major metabolites on day 1 after a single dose of 829
mg/m² in six cancer patients. Figs. 2 and 3 illustrate the same
data graphically. Statistical analyses do not show deviation from
linearity for these or any other measured parameters (data not
shown), but in view of the small numbers involved in each dose
and the degree of inter-patient variability, this conclusion
should be interpreted with caution.

The effect of leucovorin on the pharmacokinetics of capeci-
tabine and its metabolites was investigated by comparing the
results without leucovorin (day 1) and with leucovorin (day 14),
using the pharmacokinetic parameters estimated after doses of
829 and 1000 mg/m². There was no significant difference in any
of these parameters (Table 7). The intrapatient pharmacokinetic
variability was estimated from the ANOVA used to compare the
pharmacokinetic results obtained with and without leucovorin
(Table 7). The intrapatient variability (CV, %) in AU C was 26%,
8.3%, 7.4%, 78%, 84%, and 5.5% for intact drug, 5’-DFCR,
5’-DFUR, 5-FU, FUH₂, and FBAL, respectively.

DISCUSSION

5-FU has been the mainstay of treatment in a number of
cancers, notably colorectal cancer, for the last 40 years (6).
Capecitabine is a rationally designed selectively tumor-activated
fluoropyrimidine carbamate. Capecitabine itself is not cytotoxic
but is ultimately metabolized to 5-FU in tumor tissue (16). This
study has demonstrated the feasibility of both continuous and
intermittent therapy when the compound is given along with a
standard dose of p.o. leucovorin. The MTD for continuous
administration was 1004 mg/m²/day; for the intermittent sched-
ule (2 weeks on, 1 week off), the MTD was 2000 mg/m²/day.
The dose-limiting adverse events of this combination were
predictably similar to those associated with infusional regimens
of 5-FU, namely hand foot syndrome and diarrhea (6, 7). This
combination was almost devoid of hematological toxicity,
which should facilitate its acceptability to patients and clini-
cians. The adverse events that were observed in this study were
mainly of a minor nature, particularly at the recommended
Phase II dose, with many resolving in the planned 1-week rest
period in each 3-week cycle of therapy. Simple dose-adjustment
guidelines were adopted in this protocol and have gone on to be
applied in additional studies of capecitabine. None of the ob-
served adverse events attributable to drug therapy were life
threatening and all of them proved manageable in this Phase I
setting.

It is noteworthy that, in this setting of refractory cancers,
evidence of antitumor efficacy was seen, in particular in 3 of 13
patients with colorectal cancer. The parallel Phase I studies of
single-agent capecitabine have also shown promising antitumor

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Drug-related grade III–IV (NCIC-CTC) adverse events per dose level within 42 days of the start of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>No. of patients</td>
</tr>
<tr>
<td>1004c</td>
<td>6</td>
</tr>
<tr>
<td>1004i</td>
<td>6</td>
</tr>
<tr>
<td>1657</td>
<td>6</td>
</tr>
<tr>
<td>2000</td>
<td>7</td>
</tr>
<tr>
<td>2510</td>
<td>6</td>
</tr>
</tbody>
</table>

protocol. In an attempt to maximize the exposure to capecitabine
and in view of the large step between 1657 and 2510 mg/m²/day,
it was decided to explore an intermediate dose of 2000
mg/m²/day. Of the seven patients entered at this dose level, one
had grade 3 diarrhea and two had grade 3 hand-foot syndrome;
however the criteria for MTD had been achieved. All of the
adverse events observed tended to be more common and more
severe with increasing duration of exposure to capecitabine.
However, low-grade toxicities such as mild hand-foot syn-

drome, nausea, and stomatitis tended to improve or resolve
completely during the 1-week treatment-free intervals.

Only one patient (at dose level 2000 mg/m²/day) experi-
enced clinically relevant myelosuppression during the study.
On day 7, she experienced grade 3 decreases in absolute granulo-
cytes, neutrophils, and total leukocyte counts. These were con-
sidered to be disease related by the investigator. The patient was
withdrawn from the study, and these events were still ongoing at
follow-up approximately 45 days after the end of treatment. No
grade 2–4 thrombocytopenia was observed in this study.

Three patients had grade 3–4 transient increases from
baseline in total bilirubin levels. In all of the three, the baseline
bilirubin was normal. In one patient, this was associated with
raised transaminases and attributable to biliary infection second-
ary to blockage of an indwelling biliary stent. Two additional
patients had elevated aspartate aminotransferase levels at enrol-
ment and experienced one episode each of transient elevations
from baseline ≤ grade 2.

The MTD for the continuous regimen was 1004 mg/m²/day
of capecitabine. The MTD on the intermittent schedule was
2000 mg/m²/day of capecitabine, with three of seven patients
experiencing grade three adverse events; (a) diarrhea in one; (b)
PPE in one with unrelated lethargy; and (c) PPE in one at day 82
(this was outside our strict definition of adverse events occur-
ing in the first six weeks and is therefore not shown in Table 5).
The recommended dose for Phase II evaluation was, therefore,
1650 mg/m²/day of capecitabine plus leucovorin 60 mg/day
given for 2 weeks of every 3.

Therapeutic Responses. A total of three patients
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(a) a 72-year-old male with previously treated lung and liver
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tabine and its metabolites was investigated by comparing the
results without leucovorin (day 1) and with leucovorin (day 14),
using the pharmacokinetic parameters estimated after doses of
829 and 1000 mg/m². There was no significant difference in any
of these parameters (Table 7). The intrapatient pharmacokinetic
variability was estimated from the ANOVA used to compare the
pharmacokinetic results obtained with and without leucovorin
(Table 7). The intrapatient variability (CV, %) in AU C was 26%,
8.3%, 7.4%, 78%, 84%, and 5.5% for intact drug, 5’-DFCR,
5’-DFUR, 5-FU, FUH₂, and FBAL, respectively.

DISCUSSION

5-FU has been the mainstay of treatment in a number of
cancers, notably colorectal cancer, for the last 40 years (6).
Capecitabine is a rationally designed selectively tumor-activated
fluoropyrimidine carbamate. Capecitabine itself is not cytotoxic
but is ultimately metabolized to 5-FU in tumor tissue (16). This
study has demonstrated the feasibility of both continuous and
intermittent therapy when the compound is given along with a
standard dose of p.o. leucovorin. The MTD for continuous
administration was 1004 mg/m²/day; for the intermittent sched-
ule (2 weeks on, 1 week off), the MTD was 2000 mg/m²/day.
The dose-limiting adverse events of this combination were
predictably similar to those associated with infusional regimens
of 5-FU, namely hand foot syndrome and diarrhea (6, 7). This
combination was almost devoid of hematological toxicity,
which should facilitate its acceptability to patients and clini-
cians. The adverse events that were observed in this study were
mainly of a minor nature, particularly at the recommended
Phase II dose, with many resolving in the planned 1-week rest
period in each 3-week cycle of therapy. Simple dose-adjustment
guidelines were adopted in this protocol and have gone on to be
applied in additional studies of capecitabine. None of the ob-
served adverse events attributable to drug therapy were life
threatening and all of them proved manageable in this Phase I
setting.

It is noteworthy that, in this setting of refractory cancers,
evidence of antitumor efficacy was seen, in particular in 3 of 13
patients with colorectal cancer. The parallel Phase I studies of
single-agent capecitabine have also shown promising antitumor
activity in colorectal and breast cancer, with both continuous and intermittent dose schedules (9, 10). In these studies, identical patterns of toxicity were observed. A randomized Phase II study in advanced colorectal cancer has been conducted to compare the three capecitabine dose schedules: (a) 1331 mg/m²/day continuous; (b) 2510 mg/m²/day intermittent; and (c) 1657 mg/m²/day intermittent with leucovorin. Again, promising response rates have been reported with each schedule (17). The pharmacokinetics of capecitabine indicate rapid and consistent GI absorption, followed thereafter by stepwise conversion into active metabolites including 5-FU (18). Subsidiary clinical studies (16) have demonstrated that 5-FU is preferentially found in tumor tissue, as predicted by the in vitro studies of the metabolic activation of capecitabine; this may in part explain the tumor responses seen in colorectal patients whose tumors have been resistant to standard regimens of 5-FU and folinic acid. The addition of leucovorin had no significant influence on the pharmacokinetic behavior of capecitabine, and, likewise, the administration of capecitabine had no effect on the pharmacokinetics of leucovorin (data not shown).

After the administration of capecitabine, concentrations of 5-FU in plasma are low (Figs. 2 and 3). These concentrations of 5-FU can be compared with those reported in the literature after i.v. infusion of 5-FU. Although inconsistent results have been reported in the literature about plasma concentrations of 5-FU after administration of 5-FU as i.v. infusion (16), it appears that the plasma concentrations of 5-FU are lower after administration of capecitabine. Findlay et al. (19) reported a median value of 0.22 µg/mL for steady-state plasma concentrations of 5-FU after administration of 5-FU continuous infusion (300 mg/m²/day). After the administration of capecitabine at the recommended dose for Phase 2, 5-FU concentrations in plasma (AUC) are approximately eight times lower than those observed after 5-FU infusion (16).

A number of other p.o. fluoropyrimidine analogues or modulators of 5-FU are in various stages of clinical development. This group of compounds have some fundamental conceptual and practical differences. As yet, there have been no published clinical comparisons between these compounds. The dihydropyrimidine dehydrogenase inhibitor 5-eniluracil is being developed by GlaxoWellcome; it acts by inhibiting the catabolic breakdown of 5-Hi. Welicome; it acts by inhibiting the catabolic breakdown of 5-Hi.

### Table 6: Descriptive statistics on the pharmacokinetic parameters obtained after the first administration of capecitabine (829 mg/m²) on day 1 in six cancer patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Capecitabine</th>
<th>5'-DFCR</th>
<th>5'-DFUR</th>
<th>5-FU</th>
<th>FUH₂</th>
<th>FBAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cₘₐₓ (µg/ml)</td>
<td>3.32 (102%)</td>
<td>4.23 (77%)</td>
<td>4.11 (60%)</td>
<td>0.216 (63%)</td>
<td>0.311 (91%)</td>
<td>4.68 (9%)</td>
</tr>
<tr>
<td>Tₘₐₓ (h)</td>
<td>1.00 (0.50-3.00)</td>
<td>1.00 (0.50-4.00)</td>
<td>1.00 (0.50-4.00)</td>
<td>2.00 (1.00-3.00)</td>
<td>2.00 (1.00-4.00)</td>
<td>2.00 (2.00-5.00)</td>
</tr>
<tr>
<td>AUC₀₋ₐ (µg · h/ml)</td>
<td>3.98 (42%)</td>
<td>8.01 (46%)</td>
<td>7.35 (35%)</td>
<td>0.364 (42%)</td>
<td>0.476 (275%)</td>
<td>20.0 (9%)</td>
</tr>
<tr>
<td>AUC₀₋ₐ (µg · h/ml)</td>
<td>5.03 (124%)</td>
<td>8.21 (46%)</td>
<td>7.42 (35%)</td>
<td>0.370 (81%)</td>
<td>NC</td>
<td>22.7 (12%)</td>
</tr>
<tr>
<td>tₘₐₓ (h)</td>
<td>0.64 (71%)</td>
<td>0.95 (39%)</td>
<td>0.59 (18%)</td>
<td>0.78 (39%)</td>
<td>NC</td>
<td>2.43 (16%)</td>
</tr>
</tbody>
</table>

Note: NC, not calculated.
Table 7  Pharmacokinetic parameters of 5’-DFUR estimated without LV* (day 1) and with LV (day 14) in cancer patients after administration of 829 and 1000 mg/m², respectively

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without LV (day 1)</th>
<th>With LV (day 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of 829 mg/m² (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/m liter)</td>
<td>3.84 (65%)</td>
<td>3.87 (67%)</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>1.00 (0.50-4.00)</td>
<td>2.00 (0.32-3.00)</td>
</tr>
<tr>
<td>AUC0-∞ (µg · h/m liter)</td>
<td>7.19 (38%)</td>
<td>6.86 (37%)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.56 (13%)</td>
<td>0.63 (14%)</td>
</tr>
<tr>
<td>Dose of 1000 mg/m² (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/m liter)</td>
<td>6.17 (27%)</td>
<td>5.81 (39%)</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>2.00 (1.00-2.00)</td>
<td>2.00 (0.50-3.08)</td>
</tr>
<tr>
<td>AUC0-∞ (µg · h/m liter)</td>
<td>10.56 (20%)</td>
<td>11.25 (28%)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.70 (14%)</td>
<td>0.67 (24%)</td>
</tr>
</tbody>
</table>

*LV, Leucovorin.

Squibb. Tegafur is a prodrug of 5-FU, whereas uracil is a competitive inhibitor of 5-FU catabolism. The molar ratio of 4:1 has been shown to be optimal in terms of tumorblood ratios of 5-FU in experimental animals, and the compound has shown impressive response rates in Phase II trials (21). It is now incorporated in an ongoing National Surgical Adjuvant Breast and Bowel Project protocol (NSABP CO-6).

The recommended Phase II dose for this compound is 1650 mg/m²/day of capecitabine when given in combination with leucovorin (60 mg/day) taken for 14 of every 21 days. This regimen has been further explored in the first-line treatment of advanced and/or metastatic colorectal cancer (17) confirming the adverse event profile and the antitumor efficacy. Phase III evaluation for colorectal cancer versus the Mayo regimen of 5-FU and folinic acid has now completed recruitment, and results are eagerly awaited. Capecitabine has recently been approved for use in the United States by the Food and Drug Administration in the setting of advanced breast cancer that is resistant to both anthracycline and paclitaxel therapy. This accelerated approval was granted after demonstration of an objective response rate of 20% in this patient group.

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A Phase I study of capecitabine in combination with oral leucovorin in patients with intractable solid tumors.

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