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European Journal of Cancer 38 (2002) S3–S9

European Journal of Cancer

www.ejconline.com

Rational development of capecitabine

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Received 25 June 2001; received in revised form 26 November 2001; accepted 30 November 2001

Abstract

Capecitabine is a fluoropyrimidine carbamate that was rationally designed as an oral drug capable of mimicking continuous infusion 5-fluorouracil (5-FU) and delivering 5-FU preferentially to tumour tissue. Following extensive absorption, capecitabine is rapidly converted to 5-FU via a three-step enzymatic pathway. The final step depends on thymidine phosphorylase, an enzyme present at higher concentrations in malignant compared with normal tissue. This results in the delivery of 5-FU preferentially to the tumour site. Capecitabine has demonstrated high activity in preclinical xenograft models for a wide range of human solid tumours, including those resistant to 5-FU. Phase I studies have determined the maximum tolerated dose (MTD) of capecitabine and identified a number of dosage regimens, which were subsequently evaluated in a randomised, phase II study as first-line treatment for metastatic colorectal cancer. This established an intermittent regimen of capecitabine 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period as the most appropriate regimen for further clinical development. © 2002 Published by Elsevier Science Ltd.

Keywords: Capecitabine; Pharmacodynamics; Pharmacokinetics; Fluoropyrimidine; Thymidine phosphorylase

1. Introduction

Fluoropyrimidines, and in particular 5-fluorouracil (5-FU), have been in use for more than 40 years and remain central to chemotherapeutic regimens used to treat numerous solid tumours, including breast, colorectal and head and neck cancers. Bolus administration (weekly, or a 5-day course every 4–5 weeks) was the preferred schedule in the 1960s and 1970s, and in combination with leucovorin remains one of the most used regimens in advanced or metastatic colorectal cancer. However, 5-FU concentrations rapidly fall below the cytotoxic threshold because of the relatively short plasma elimination half-life (10–20 min) of this drug [1,2], thus limiting the efficacy of 5-FU.

During the 1980s, various attempts were made to modulate 5-FU in colorectal cancer through combination with other agents, such as leucovorin, levamisole, methotrexate, interferon-α or N-(phosphonacetyl)-L-aspartate (PALA) [3]. Another approach has been to intensify the dose by administering 5-FU as a continuous or protracted infusion over 5 days or more. Continuous infusion became more popular with the availability of ambulatory infusion pumps and various central venous catheter systems, and has become standard therapy at many centres for the treatment of head and neck, oesophageal, rectal and anal cancers. Recent clinical data also strongly support the use of continuous infusion 5-FU in breast and colon cancer. In a review of studies in metastatic breast cancer [4], continuous infusion 5-FU was found to produce an average overall response rate of 29% across studies (range 12–54%): most of these studies were in heavily pretreated patients in whom continuous infusion 5-FU was administered as second- or third-line chemotherapy. In a more recent study [5], a 20% overall response rate was reported for third-line continuous infusion 5-FU in metastatic breast cancer patients who had been pretreated with intravenous (i.v.) bolus 5-FU. When used as pre-operative/neo-adjuvant therapy in 123 treatment-naïve patients with operable breast cancer, continuous infusion 5-FU in combination with epirubicin plus cisplatin produced a 96% overall response rate and 78% 5-year survival [6]. In randomised trials in advanced colorectal cancer, continuous infusion of 5-FU either with or without leucovorin resulted in higher response rates and/or survival benefit compared with i.v. bolus 5-FU [7–10]. These findings have been confirmed in a meta-analysis of six randomised trials in

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0959-8049/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0959-8049(01)00414-2

colorectal cancer, which showed superior overall response rates (22% versus 14%, $P = 0.0002$) and median survival duration (12.1 versus 11.3 months, $P = 0.04$) [11]. Nevertheless, the difference in median survival duration, although statistically significant (owing to the large sample size), was modest. The meta-analysis also revealed that continuous infusion 5-FU produced a significantly lower incidence of grade 3-4 haematological toxicity (4% versus 31%, $P < 0.0001$), but a higher incidence of hand–foot syndrome (34% versus 13%, $P < 0.0001$) compared with bolus 5-FU [12].

Recently, a number of oral fluoropyrimidines have been developed in response to the need for a more convenient agent with an improved safety profile and equivalent/superior efficacy compared with i.v. 5-FU [13–19]. Oral administration has the advantage of permitting convenient, patient-orientated therapy, providing the patient with a degree of independence and improved quality of life while avoiding many of the complications associated with i.v. drug administration [20]. Furthermore, most patients prefer orally administered therapy to i.v. treatment [21,22]. One such orally administered fluoropyrimidine derivative is capecitabine, which was rationally designed to generate 5-FU preferentially at the tumour site with the objective of improving the risk:benefit ratio of fluoropyrimidine therapy. The aim of this article is to outline the rational development of capecitabine from *in vitro* and preclinical studies to phase I and II clinical trials.

2. Preclinical studies

Capecitabine is converted to 5-FU via a sequential triple enzymatic pathway that exploits the higher concentrations of the enzyme thymidine phosphorylase (TP) present in tumour tissue (Fig. 1). Following rapid and almost complete absorption of the intact molecule from the gastrointestinal tract [23], capecitabine is converted to 5′-deoxy-5-fluorocytidine (5′-DFCR) by the hepatic enzyme, carboxylesterase. 5′-DFCR is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by the enzyme cytidine deaminase, which is present in both the liver and tumour tissue. The third and final step is conversion of 5′-DFUR preferentially within the tumour to form active 5-FU. This final stage relies on TP, a tumour-associated angiogenic factor which appears identical to platelet-derived endothelial cell growth factor [24–26]. TP expression is correlated with the intensity of angiogenesis, enhanced tumour growth and invasion, and poor prognosis [27,28]. TP has also demonstrated anti-apoptotic properties [29]. A study by Miwa and colleagues found that TP activity in human tumour tissue is 3–10 times higher than in corresponding normal tissue. This was true for a range of tissue types, including colorectal, gastric, breast, cervical, uterine, ovarian, renal, bladder and thyroid tumours and liver metastases from colorectal tumours [30]. The notable exception was the liver. Further preclinical investigation has demonstrated that tumour tissue concentrations of TP, and more particularly the ratio of TP to dihydropyrimidine dehydrogenase, is a significant predictor of sensitivity to capecitabine [31]. This ability to predict sensitivity has not been observed with other oral fluoropyrimidines to date, and potentially enables the individualisation of treatment according to a patient's biochemical prognostic markers.

Preclinical studies in 23 human cancer xenograft models in athymic mice demonstrated that capecitabine induced $>50\%$ tumour inhibition in 75% of tumour

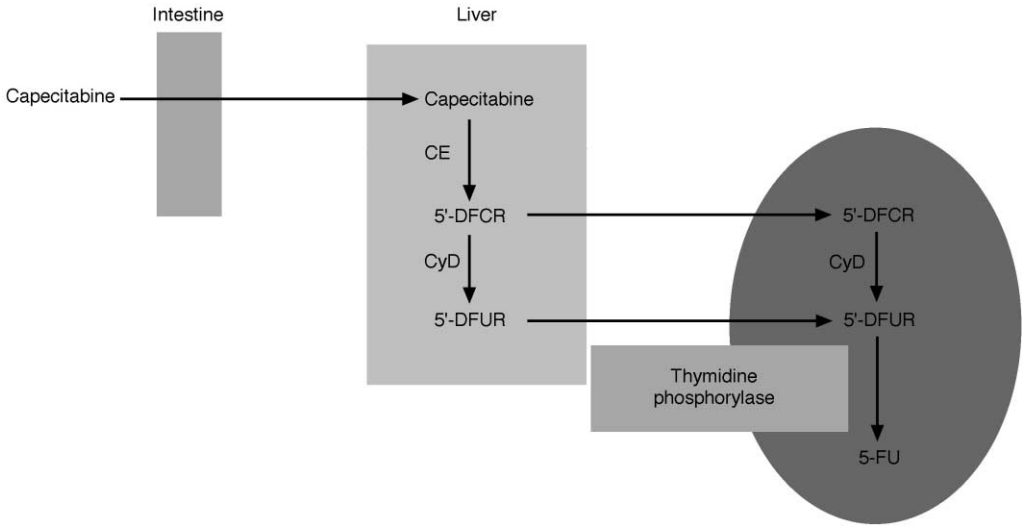

Fig. 1. Enzymatic activation of capecitabine. 5-FU, 5-fluorouracil; 5′-DFCR, 5-′-deoxy-5-fluorocytidine; CE, carboxylesterase; 5′-DFUR; 5′-deoxy-5-fluorouridine; CyD, cytidine deaminase.

models tested compared with 21 and 4% for UFT (uracil plus tegafur) and 5-FU, respectively, when administered at their maximum tolerated doses (MTDs) [32]. These models included a range of human cancer xenografts, including colon, gastric, breast, cervical, bladder and ovarian tumours. Fig. 2 shows an example of the tumour growth inhibition induced by capecitabine compared with that produced by UFT or 5-FU in five different human breast cancer xenografts [32]. In addition, effective tumour growth inhibition was achieved with capecitabine in models that were resistant to both 5-FU and UFT [31,33].

Further studies in mouse xenograft models of human breast and colon cancers have shown that exposure to paclitaxel, docetaxel, mitomycin C or cyclophosphamide increased tumour TP concentrations by 4–8-fold within 8–14 days of administration [34,35]. X-ray irradiation has also been shown to enhance TP expression markedly within tumour tissue but not in healthy tissue in a number of mouse xenograft models of human cancers [36]. Thus, there is a clear rationale for administration of capecitabine in combination with cytotoxic therapies known to upregulate TP, which will be discussed further elsewhere in this supplement [37].

The tumour selectivity of capecitabine has been confirmed in a study of 19 colorectal cancer patients scheduled for surgery of their primary tumour and/or liver metastases [38]. Patients received capecitabine 1255 mg/m^2 twice daily for 5–7 days before tumour resection. Mean 5-FU concentrations were 3.2 times higher in tumour tissue than in surrounding normal tissues ($P = 0.002$), confirming results of xenograft studies that demonstrated the tumour-selective activation of capecitabine [30,31].

3. Pharmacokinetic studies

Capecitabine is rapidly and almost completely absorbed and converted to its metabolites following the oral administration of single doses in cancer patients [23,39–41]. Two hours after oral administration, mean maximum plasma concentration (C_{max}) for capecitabine was 2.7–4.0 μg/ml and its elimination half-life ranged from 0.6–0.8 h [42]. C_{max} for the metabolites 5′-DFCR, 5′-DFUR and 5-FU was also reached approximately 2 h after administration [42]. Fig. 3 shows an example of the rapid increase in mean plasma concentrations of capecitabine and three of its metabolites in 25 cancer patients after a single oral dose of 2000 mg/m^2 [39,42]. The mean elimination half-life of α-fluoro-β-alanine (FBAL), the final catabolite of 5-FU, is longer, ranging from 2.6 to 11.5 h. Approximately 96% of the administered dose of capecitabine is recovered as metabolites in urine, primarily as FBAL [23].

There is no indication that capecitabine or its primary metabolites 5′-DFCR and 5′-DFUR accumulate in plasma after chronic dosing every 12 h [43]. The area under the concentration curve (AUC) of 5-FU increased by 10–60% during multiple dosing, but plasma concentrations of 5-FU declined to undetectable concentrations within 12 h of the previous dose.

Protein plasma binding of capecitabine and the three metabolites 5′-DFCR, 5′-DFUR and 5-FU is relatively low at 54, 10, 60 and 10%, respectively [42]. This low degree of protein binding favours tissue penetration and indicates a low potential for drug interaction caused by displacement from protein binding sites. The effect of food on the pharmacokinetics of capecitabine (666 or 1255 mg/m^2 twice daily) was examined in a randomised,

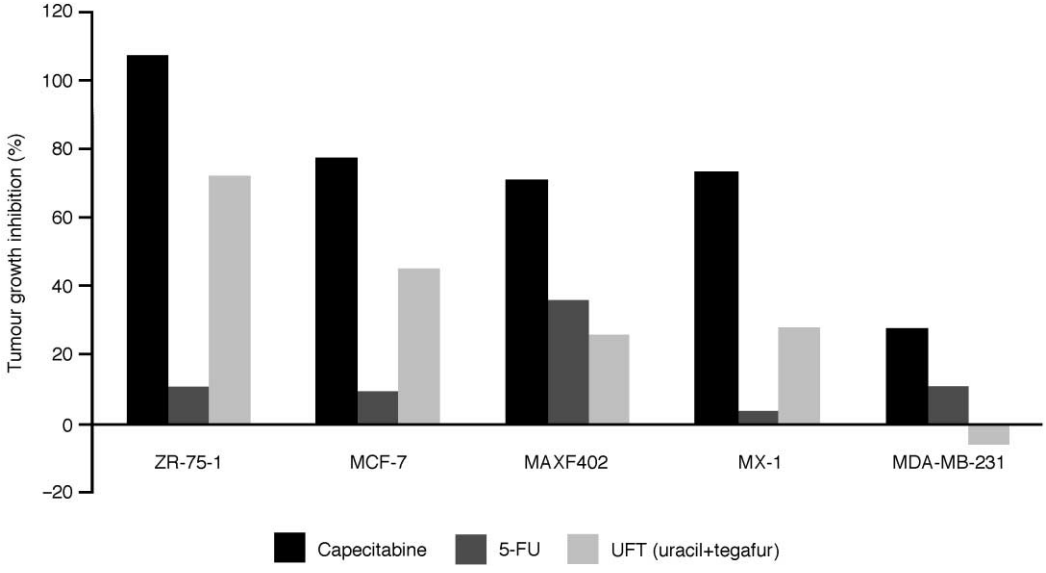

Fig. 2. Comparative tumour growth inhibition of capecitabine, uracil plus tegafur (UFT) and 5-fluorouracil (5-FU) administered at their maximum tolerated doses in five human breast cancer xenograft models.

crossover study in 11 patients with advanced colorectal cancer [40]. Plasma concentrations of capecitabine and its metabolites were determined following oral administration of capecitabine on days 1 and 8 either after overnight fasting or following a standard breakfast. Compared with the fasting state, food significantly decreased the C_{max} for capecitabine, 5′-DFCR, 5′-DFUR and 5-FU. Fasting also significantly increased the AUC for capecitabine and 5′-DFCR, but had little effect on the AUC of the key metabolite, 5-FU. As patients in all studies have received capecitabine following a meal, it is recommended that capecitabine is administered within 30 min after food (breakfast and dinner), with water.

The pharmacokinetics of capecitabine have also been compared following oral administration of a single dose of capecitabine 1250 mg/m^2 in 14 patients with normal liver function and 13 with mild to moderate hepatic dysfunction caused by liver metastases [41]. No significant differences in the pharmacokinetic parameters of the main metabolites (5′-DFUR, 5-FU and FBAL) were seen in patients with hepatic impairment compared

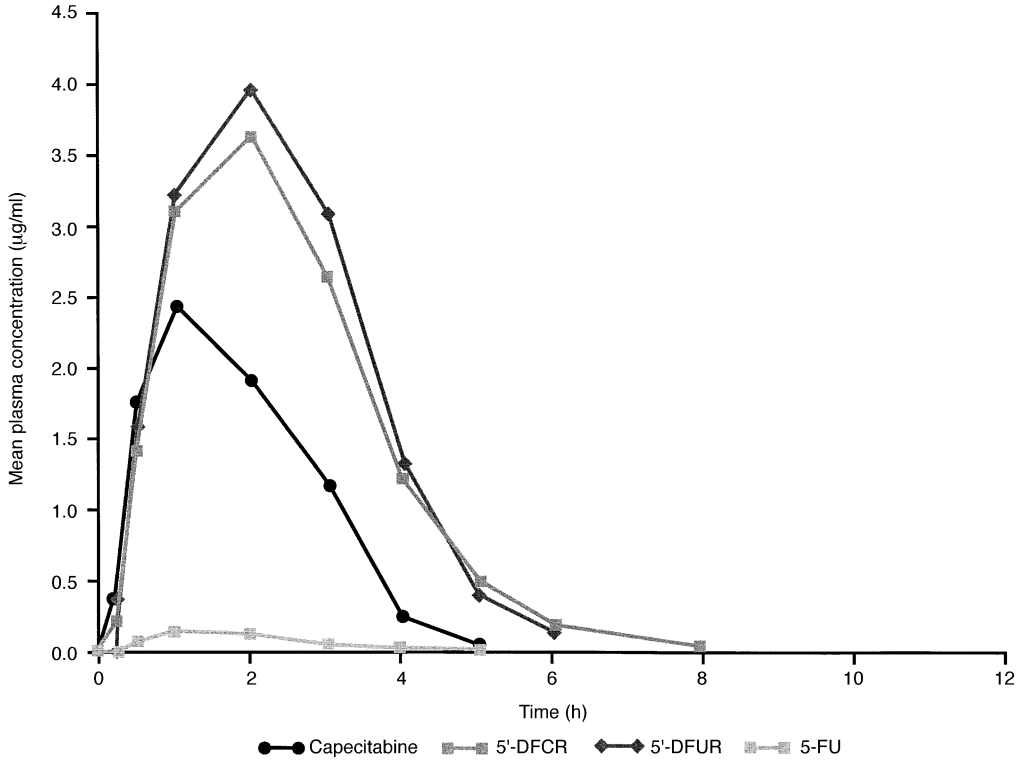

Fig. 3. Mean plasma concentrations of capecitabine, 5′-deoxy-5-fluorocytidine (5′-DFCR), 5′-deoxy-5-fluorouridine; 5′-DFUR and 5-fluorouracil (5-FU) after oral administration of a single dose of capecitabine 2000 mg to 25 cancer patients.

Table 1
Summary of the design and main results of phase I clinical trials of capecitabine in patients with advanced/metastatic colorectal cancer

Study	Europe [47]	USA [43]	Europe [46]
Treatment	Intermittent capecitabine	Continuous capecitabine	Continuous/intermittent capecitabine with leucovorin[a]
No. of patients	34	33	31 (6/25)
Dose levels	6	6	1/4
MTD (mg/m^2 twice daily)	1500	828	502/1000
Phase II dose (mg/m^2 twice daily)	1250	666	NA/825
DLT	Diarrhoea Hypotension Leucopenia	Diarrhoea	Diarrhoea Nausea/vomiting Hand–foot syndrome Asthenia
Median treatment duration: days (range)	85 (14–833+)	43 (18–594+)	52/87 (NA)

MTD, maximum tolerated dose; DLT, dose-limiting toxicity; NA, not available.

[a] Data for patients receiving continuous or intermittent regimen capecitabine are presented separately, with continuous schedule data appearing first.

with patients with normal hepatic function. Therefore, it was concluded that no *a priori* dose adjustment would be required in such patients, although caution should be exercised during administration of capecitabine in patients with hepatic dysfunction. Creatinine clearance has no effect on the pharmacokinetics of 5′-DFUR and 5-FU in patients with mild to moderate renal impairment, but the AUC of FBAL was increased by 45% if the creatinine clearance was reduced by 50% [44]. Based on data from phase III studies, capecitabine is contraindicated on patients with severe renal impairments (calculated creatinine clearance <0.5 ml/s).

In 12 patients with metastatic tumours of various origins, the co-administration of the antacid Maalox® with a single oral dose of capecitabine 1250 mg/m^2 had no significant effect on the pharmacokinetics of capecitabine or its metabolites compared with the administration of the same dose of capecitabine alone [45]. There is no evidence of pharmacokinetic interactions between capecitabine and leucovorin, docetaxel or paclitaxel [42].

4. Phase I and II clinical trials in metastatic colorectal cancer

A series of phase I clinical trials has been undertaken in Europe and the USA. These trials have evaluated continuous and intermittent capecitabine treatment as monotherapy and in combination with leucovorin. The design and main results of phase I clinical trials of capecitabine in patients with solid tumours are summarised in Table 1 [43,46,47]. Following completion of these phase I trials, which demonstrated promising antitumour activity, a randomised, phase II study of capecitabine as first-line treatment in metastatic colorectal cancer was undertaken to define the most appropriate regimen for further investigation.

The phase II study enrolled a total of 109 patients with metastatic/advanced colorectal cancer who had not received prior chemotherapy [48]. Patients were randomised to one of three treatment groups: continuous capecitabine 666 mg/m^2 twice daily ($n=39$), intermittent capecitabine 1255 mg/m^2 twice daily for 14 days followed by a 7-day rest period ($n=35$), or intermittent capecitabine 828 mg/m^2 twice daily plus leucovorin 30 mg twice daily for 14 days followed by a 7-day rest period ($n=35$) (Fig. 4). The number of confirmed tumour responses in the intent-to-treat population was similar for the three treatment groups (Table 2). Most responses were observed after 6 weeks of therapy and occurred at all disease sites, particularly the liver. The group receiving intermittent capecitabine without leucovorin had the longest median time to disease progression (7.5 months) compared with the other two groups (4.2 and 5.4 months in the continuous monotherapy and leucovorin combination therapy groups, respectively). The overall response rate of 24% with intermittent capecitabine compares favourably with response rates for 5-FU plus leucovorin in patients with metastatic colorectal cancer. The addition of leucovorin to the intermittent regimen required a

Table 2
Efficacy of capecitabine in the randomised, phase II clinical trial in patients with metastatic colorectal cancer

	Continuous capecitabine ($n=39$)	Intermittent capecitabine ($n=34$[a])	Intermittent capecitabine with leucovorin ($n=35$)
Objective response rate (%) (95% CI)	21 (9–36)	24 (11–41)	23 (10–40)
Complete response (confirmed) (%)	5	3	6
Partial response (confirmed) (%)	15	21	17
Stable disease (%)	51	62	63
Progressive disease (%)	21	9	9
Median time to disease progression (months) (95% CI)	4.2 (2.8–7.0)	7.5 (4.0–9.0)	5.4 (2.9–5.7)

95% CI, 95% confidence interval.
[a] One patient withdrew consent prior to receiving medication.

Table 3
Major toxicities in the randomised, phase II clinical trial of capecitabine in patients with metastatic colorectal cancer

Grade 3[a] adverse events	Continuous capecitabine ($n=39$)	Intermittent capecitabine ($n=34$)	Intermittent capecitabine with leucovorin ($n=35$)
Diarrhoea (%)	5	6	20
Stomatitis (%)	0	3	3
Abdominal pain/colic (%)	0	3	9
Nausea (%)	3	0	3
Vomiting (%)	3	6	6
Hand-foot syndrome (%)	10	15	23

[a] Only 1 patient experienced grade 4 adverse events (diarrhoea and vomiting, intermittent capecitabine monotherapy group).

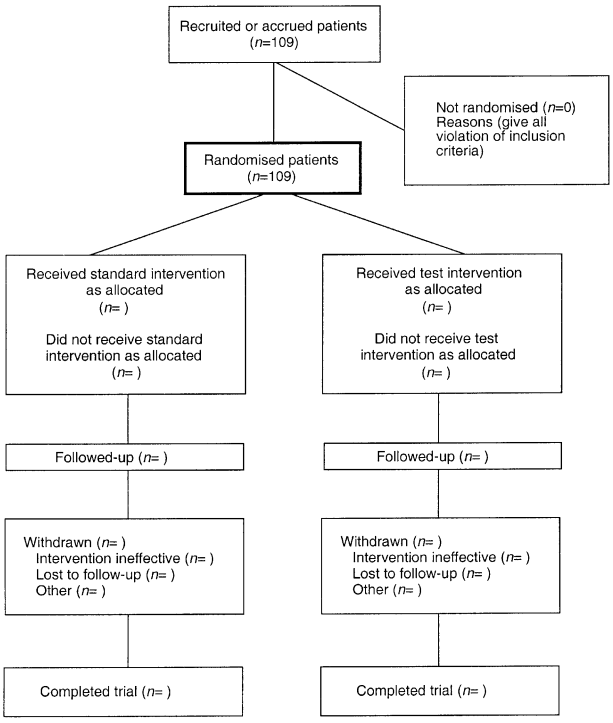

Fig. 4. Flow chart of the progress of patients through the trial (adapted from Ref. [50]).

reduction in the capecitabine dose intensity, did not result in improved efficacy and was associated with more toxicity. All three treatment schedules were generally well tolerated: the major toxicities are shown in Table 3. The intermittent regimen consisting of capecitabine 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period was selected for further clinical development based on its favourable efficacy:toxicity ratio, higher dose intensity and superior therapeutic index compared with the other regimens. Additionally, the 7-day drug-free period is considered appealing to patients. The results of randomised, phase III trials in metastatic colorectal cancer comparing the intermittent monotherapy regimen with the Mayo Clinic regimen of i.v. bolus 5-FU plus leucovorin are discussed in the article by Twelves later in this supplement [49].

5. Conclusions

Capecitabine is a novel, oral fluoropyrimidine that was rationally designed to mimic continuous infusion 5-FU and deliver 5-FU preferentially to the tumour site. Preclinical studies have confirmed the anti-tumour activity of capecitabine in a wide range of xenograft models of various human cancers and have provided the rationale for combination with other cytotoxic agents. Pharmacokinetic studies have established the metabolism of the parent compound and its active and inactive metabolites in humans. Phase I studies have determined the maximum tolerated dose of capecitabine and identified a number of dosage regimens which were studied in more detail in patients with advanced/metastatic colorectal cancer. A randomised, phase II study in patients with metastatic colorectal cancer identified the intermittent regimen consisting of capecitabine 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period as the most appropriate for further development based on its favourable time to disease progression, higher dose intensity and superior therapeutic index compared with other regimens. This regimen has subsequently been evaluated in phase II trials in metastatic breast cancer and phase III trials in metastatic colorectal cancer.

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