Capecitabine: an overview of the side effects and their management

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Xeloda (capecitabine), a thymidine phosphorylase activated fluoropyrimidine carbamate, is currently the only universally approved orally administered 5-fluorouracil (5-FU) prodrug. It belongs to a newer generation of orally administered fluoropyrimidines. It has been developed because of the clinical need for efficient, tolerable and convenient agents, which do not require continuous infusion. Capecitabine is not a cytotoxic drug in itself, but via a three-step enzymatic cascade, it is converted to 5-FU mainly within human cancer cells. While the drug compares favorably with 5-FU in patients with advanced or metastatic colorectal cancer and pretreated breast cancer, it also has an improved toxicity profile, mainly of gastrointestinal and dermatologic effects with a significantly lower incidence of grade 3/4 myelotoxicity compared with infusional 5-FU-based chemotherapy. Capecitabine's selective activation within the tumor allows for less systemic toxicity events. A gradient of fluoropyrimidine toxicity is observed: high in the US and low in East Asia. In addition, there is a discrepancy in tolerance of dose among patients treated in the US vs. Europe. Although patients can take the drug orally in the convenience of their own home, the key to successful management of capecitabine is the clinician's awareness of its severe, but low in incidence, adverse effects, and the patients' education, emphasizing compliance with the treatment plan, prevention and timely recognition of its toxicities. *Anti-Cancer Drugs* 19:447–464 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Fluoropyrimidines remain the standard treatment regimens for numerous types of solid tumors. Capecitabine (Xeloda, Hoffmann-La Roche Inc., Nutley, New Jersey, USA), a thymidine phosphorylase (TP)-activated fluoropyrimidine carbamate, is actually the only universally approved orally administered fluoropyrimidine. It belongs to a newer generation of orally administered fluoropyrimidines. Capecitabine has been developed because of the clinical need for efficient, tolerable and convenient agents that do not require continuous infusion like the original fluorinated analog of uracil, 5-fluorouracil (5-FU).

Capecitabine's selective activity within the tumor allows for less systemic toxicity events and permits patients to administer the drug in the convenience of their own home. Capecitabine is not a cytotoxic drug in itself but, through a series of enzymatic steps, it is activated to 5-FU. Selective conversion of its final metabolite 5′-deoxy-5-fluorouridine (5′-DFUR) to 5-FU, takes place mainly within human cancer cells and in healthy liver tissue. This selective activation leads to a higher intratumoral level of active 5-FU anabolites resulting in increased antitumor activity. In clinical trials, capecitabine has proven to be an effective substitute for 5-FU in colorectal and breast cancer, and has become an accepted standard treatment in these tumors as a single agent and as a component of combination chemotherapy. Its success has also been seen in other solid tumors as well as a radiosensitizing agent. At the same time, capecitabine manifests a significantly lower incidence of serious adverse events (AEs). Grade 3/4 neutropenia and grade 3/4 nonhematological AEs – nausea, emesis, stomatitis, diarrhea – are less frequently observed when capecitabine is administered either as single-agent monotherapy or in combination with other cytotoxic agents compared with 5-FU-based chemotherapy regimens. In addition, hand–foot syndrome (HFS) secondary to capecitabine administration and hyperbilirubinemia are more frequently observed with capecitabine.

Capecitabine, indeed, offers patients more freedom from hospital visits, and less inconvenience and complications associated with infusion devices. Although its toxicity profile is manageable, it requires the recognition of the infrequently, but potentially serious, AEs by the patient and prompt intervention by the clinician.

Pharmacodynamics and pharmacokinetics

General

Capecitabine {*N*-[1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyridinyl]-*n*-pentyl carbamate}, a rationally

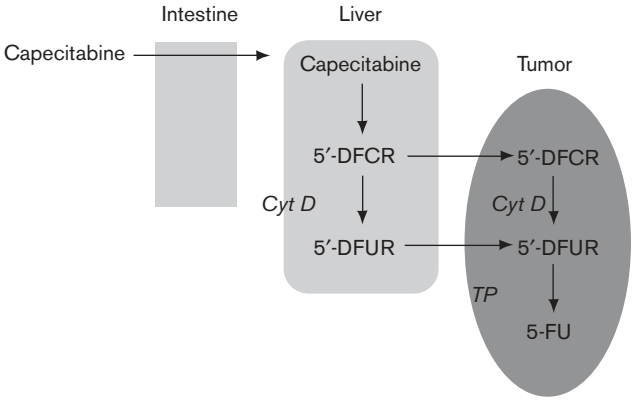
designed orally administered flouroupirimidine carbamate, is a crystalline solid with a molecular weight of 359.35 kDa. It is highly soluble in water and stable in tablet form for at least 9 months [1]. After oral administration it is absorbed through the intestinal membrane as an intact molecule. After absorption, capecitabine is converted to the active compound 5-FU through a unique activation mechanism, a three-step enzymatic cascade. The first step of this enzymatic pathway takes place in the liver, where capecitabine is transformed to 5′-deoxy-5-flourocytidine (5′-DFCR) by the hepatic enzyme carboxylesterase and sequentially to 5′-DFUR by cytidine deaminase, a ubiquitous enzyme found in most tissues but in higher concentrations in healthy liver tissue, plasma in many human tumor tissues [2]. Finally, 5′-DFUR is converted to the active drug 5-FU by TP [3], an enzyme found in higher concentration in various solid tumors and in healthy liver tissue (Fig. 1) [2,4]. TP is found in tumor tissues in an amount three to one times higher than in normal adjacent tissues [5]. As a result, more of the active anticancer agent 5-FU is produced where needed, whereas exposure of most healthy tissues is reduced [3], thereby reducing the potential systemic side effects, as documented in various clinical trials [5–7]. 5-FU is either catabolized by dihydropyrimidine dehydrogenase (DPD) or anabolized by thymidine phosphorylase, and thymidine kinase. The former is responsible for detoxification and subsequent elimination, whereas the anabolic pathway forms the compounds fluorouridine triphosphate and fluorodeoxyuridine triphosphate, responsible for cytotoxic activity. 5-FU catabolism by DPD results in the formation of dihydrofluorouracil, which is then further metabolized to fluoro-β-ureidopropionic acid by dihydropyrimidinase and to fluoro-β-alanine (FBAL) by β-ureido-propionase before urinary elimination [8].

Capecitabine is almost 100% orally bioavailable and within 1.5–2 h after rapid absorption, peak plasma levels are present. Malabsorption syndrome or physical abnormality of the upper gastrointestinal tract may, however, adversely affect absorption of the drug [9,10].

A crossover study evaluated the effect of food on capecitabine pharmacokinetics in 11 patients with colorectal cancer [11]. Maximum plasma concentration (C_{max}) and area under plasma concentration time curve (AUC) were decreased after food intake, whereas time until occurrence of C_{max} values was increased. The extent of change in AUC was more profound for capecitabine, whereas the AUC of the cytotoxic drug 5-FU was moderately affected. In addition, profound influence on C_{max} of capecitabine and its metabolites was observed [11]. Although the clinical significance of food interaction should be further examined, capecitabine is still recommended to be administered within 30 min after food consumption. This time schedule is recommended by the manufacturer, and was applied in most of the clinical trials [11,12].

The elimination half-life of capecitabine is short, ranging from 0.49 to 0.89 h. The half-life for the 5-FU metabolite is slightly longer at 0.67–1.15 h. It is rapidly metabolized in the liver, which limits the build-up of the drug in the body and reduces the potential for long-term effects. As with most orally administered drugs, its metabolism gives a large variation in plasma concentrations (27–89%) between patients [13,14]. The drug, along with its

Fig. 1



Conversion of capecitabine to 5-fluorouracil (5-FU) via thymidine phosphorylase (TP). Capecitabine is orally administered, and is absorbed by the intestinal mucosal membrane as the intact molecule. A series of three enzymatic steps are required to convert this prodrug to 5-FU. The parent compound reaches the liver through the portal circulation, where it is metabolized to 5′-deoxy-5-fluorocytidine (5′-DFCR) by a 60-kDa carboxylesterase. This latter compound is converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase (Cyt D), which is widely distributed throughout the body and in plasma. Finally, 5-FU is released from 5′-DFUR through the action of TP. As many tumor tissues contain higher levels of this enzyme compared with normal tissues, formation of 5-FU may occur preferentially within tumor tissue.

metabolites, is excreted by the kidneys. Patients with moderate renal failure (creatinine clearance (ClCr) 30–50 ml/min) are recommended to receive a lower dose, 75% of the initial dose, whereas those with severe renal impairment (ClCr < 30 ml/min) should not be administered the drug, so as to avoid potentially increased risk of AEs [12,15]. The dosing in the presence of liver dysfunction is an important issue, since hepatic involvement because of metastases is common in patients being treated with capecitabine. Although the involvement of the liver with capecitabine conversion to 5-FU through hepatic TP results in hyperbilirubinemia in many cases, recently, a small study involving patients with liver dysfunction secondary to metastases demonstrated that liver dysfunction does significantly affect capecitabine absorption or metabolism [16]. In most studies, hyperbilirubinemia was defined as an isolated laboratory abnormality, most prominently affecting the indirect bilirubin. Although the exact mechanism of action is unknown, it is believed to be related either to low-grade compensated hemolytic anemia secondary to capecitabine [17] or to the liver metabolism of 5′-DFUR to 5-FU by the hepatic TP. Currently no dose adjustments are recommended in patients with liver dysfunction, although there is no available data for patients with liver dysfunction due to other causes [12,16].

Potential drug interactions

Even though there appears to be no clinically relevant interaction between capecitabine and other anticancer drugs, including paclitaxel, docetaxel and irinotecan [9,18–22], a number of other drugs, which are considered to have potential interactions with capecitabine, have been observed.

Phenytoin

The tendency for increased plasma levels of phenytoin with concomitant use of capecitabine suggests a potential interaction [23,24]. Phenytoin is principally metabolized by cytochrome P450 (CYP2C9). Inhibition of the CYP2C9-dependent phenytoin metabolism, because of the depressed expression of hepatic CYP2C9 enzymes by fluorouracil, the active metabolite of capecitabine, is the predominant hypothesis for the mechanism of interaction, as was previously observed in rats and in colorectal cancer patients [25]. Therefore, patients receiving concomitant capecitabine and phenytoin should be monitored for increased plasma levels of phenytoin as well as for any associated clinical symptom.

Warfarin

Careful monitoring of patients with the concomitant use of capecitabine and warfarin is strongly warranted. Warfarin is one of the most common oral anticoagulant agents and is metabolized by liver CYP2C9 isoenzymes. In a recent retrospective study, associated gastrointestinal bleeding with altered coagulation parameters – prolonged prothrombin time and increased international normalized ratio levels – was observed in patients simultaneously receiving these drugs [26]. Although the exact mechanism of action for interaction is not clarified, it is believed to be related to the downregulation of CYP9C9, by capecitabine or its metabolites or to a pharmacodynamic interaction with warfarin [27]. Coagulation parameters are recommended to be measured weekly in these patients with an appropriate adjustment of warfarin dose [26].

Sorivudine and brivudine

5-Bromovinyluracil, the metabolite of two antiviral agents, sorivudine or brivudine, has been known to be a potent inhibitor of DPD, the enzyme that catabolizes 5-FU [28]. Concurrent therapy of capecitabine with these antiviral agents is not recommended [12]. In fact, it is suggested that at least 4 weeks must elapse before the patient receives capecitabine therapy [12,28].

Other drugs

With respect to other drugs interactions, allopurinol, specifically its metabolite, oxypurinal, is thought to decrease 5-FU efficacy by inhibiting its conversion to 5-flurouridylate and its incorporation into tumor RNA [29]. Originally, this aimed at protecting normal tissues from 5-FU toxicities [30], but laboratory findings do not support that hypothesis [31]. Although there are no available data for the concomitant use of capecitabine and allopurinol, it is recommended that it be avoided, if possible [12].

Cimetidine, the imidazole H_2-receptor antagonist, was proven to influence 5-FU pharmacokinetics by increasing peak plasma levels and AUC, and reducing total-body clearance of 5-FU. It is believed that DPD inhibition is responsible for this interaction [32,33]. At present, no reports have been made for the interaction between capecitabine and cimetidine. As DPD participates in capecitabine metabolism, it is advisable to avoid concurrent administration of cimetidine and, if necessary, it should be substituted by ranitidine or another class of antiulcer medication [12].

Finally, early clinical studies have revealed that concurrent administration of capecitabine with leucovorin (LV) [34] and interferon-α [35] reduces the maximum tolerated dose of the former. Consequently, these combinations should be avoided or caution should be exercised when these agents are used concurrently with capecitabine [12].

Safety and tolerability of capecitabine

Capecitabine is currently approved by the US Food and Drug Administration (FDA) for treating, as first-line single-agent therapy, patients with advanced or

Table 1 Grading of the main clinical adverse events

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of >4 stools/day over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools/day over baseline; i.v. fluids indicated <24 h; moderate increase in ostomy output compared with baseline; not interfering with ADL	Increase of ≥ 7 stools/day over baseline; incontinence; i.v. fluids ≥ 24 h; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Life-threatening consequences	Death
Nausea	Loss of appetite without alterations of eating habits	Decreased oral intake without significant weight loss, dehydration or malnutrition; i.v. fluids indicated <24 h	Inadequate oral caloric or fluid intake; i.v. fluids, tube feedings, or TPN indicated ≥ 24 h	Life-threatening consequences	Death
Stomatitis	Erythema	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis, spontaneous bleeding; life-threatening consequences	Death
HFS	Dermatitis without pain	Painful erythema, not affecting patients' daily functions/activities	Very painful ulcerative dermatitis or blistering which affects patients' daily functions/ activities	N/A	N/A
Vomiting	1 time/day	2–5 times/day; i.v. fluids indicated <24 h	≥ 6 times/day; i.v. fluids or TPN indicated ≥ 24 h	Life-threatening consequences	Death

Cancer Therapy Evaluation Program, March 31, 2003, date of publication: August 9, 2006 [40].
ADL, activities of daily living; HFS, hand–foot syndrome; i.v., intravenous; N/A, not applicable; TPN, total parenteral nutrition.

metastatic colorectal cancer, when single-agent fluoropyrimidine therapy is preferred. It is also approved for use in metastatic breast cancer patients as either a single agent following resistance to both anthracycline-based and paclitaxel-based regimens or in those in whom further anthracycline treatment is contraindicated or in combination with docetaxel after the failure of earlier anthracycline-based chemotherapy. Most recently, it was approved for use in Dukes C colon cancer patients, who have complete surgical resection of the tumor, as single-agent adjuvant therapy, when treatment with fluoropyrimidine alone is preferred [36].

The FDA-approved schedule and dosing of capecitabine as single-agent therapy for metastatic colorectal and breast cancer patients is 1250 mg/m^2 twice daily (b.i.d.) for 14 days followed by 7 days rest in 3-week cycles [12]. The same schedule and dosing were approved for capecitabine as single-agent adjuvant therapy for Dukes C colon cancer patient [37,38]. For metastatic breast cancer patients, when used in combination with docetaxel, the approved schedule and dosing are 1250 mg/m^2 b.i.d., 2 weeks on/1 week off (3-week cycles) and for docetaxel 75 mg/m^2 as an 1-h intravenous (i.v.) infusion on day 1 of each 3-week cycle [20]. The drug has also been studied in patients with prostate, pancreatic, renal cell, and ovarian cancer, but has not yet been approved by the FDA [36,39].

Capecitabine, taken in tablet form, allows the patient to control administration of the drug in a home-based setting. The safety of the drug is of considerable importance, as it is still an agent associated with treatment-related side effects. Quick recognition by patients and prompt intervention by doctors prevent progression to more serious events (Table 1) [40]. In certain circumstances, the initial dose of the drug may need to be reduced. Only 75% of the normally administered initial dose should be given in patients with moderate renal dysfunction. During treatment, the initial dosage may need to be decreased anywhere from 50 up to 75% to allow prompt control and resolution of certain side effects [39].

Colorectal cancer

For more than 40 years, 5-FU has been the foundation treatment for metastatic colorectal cancer and has been used with LV or in combination with irinotecan or oxaliplatin [41]. As first-line therapy in colon cancer patients capecitabine has been studied either as single-agent administration compared directly to i.v. 5-FU/LV in two large randomized phase III trials [6,7] or in combination with irinotecan [42–45] and oxaliplatin [46–49] in noncomparative studies. In the adjuvant setting a large randomized phase III trial (X-ACT study), enrolling 1987 Dukes C colon cancer patients, was conducted comparing single-agent capecitabine administration with i.v. 5-FU/LV (Mayo Clinic regimen) [50].

In the first-line monotherapy setting, the two randomized, prospective phase III trials enrolled a total number of 1207 patients, who were randomized to receive either oral capecitabine (1250 mg/m^2 b.i.d. 2 weeks on/1 week off in 3-week cycles) or the Mayo Clinic regimen (LV 20 mg/m^2 followed by 5-FU 425 mg/m^2 i.v. bolus on days 1–5 in a 4-week cycle) [6,7]. Capecitabine demonstrated a statistically significant superior objective response rate (ORR) compared with 5-FU/LV (26 vs. 17%; $P < 0.0002$), even in patient subpopulation with poor prognostic parameters. Time to progression (TTP)

was equivalent in both arms (4.6 vs. 4.7 months; $P = 0.85$) and the same was revealed for overall survival (OS) (12.9 vs. 12.8 months; $P = 0.48$) [51]. As far as the safety profile was concerned, all-grade AEs, including diarrhea (47.7 vs. 58%; $P < 0.001$), stomatitis (24.3 vs. 61.6%; $P < 0.001$), nausea (87.9 vs. 47.6%; $P < 0.001$), alopecia (5 vs. 20.6%; $P < 0.001$) and neutropenia requiring medical intervention (1.2 vs. 10.5%; $P < 0.001$) occurred significantly more frequently in the 5-FU/LV arm. HFS was the only AE occurring in significantly higher incidence with capecitabine (55.5 vs. 62%; $P < 0.001$). In addition, grade 3/4 stomatitis (2 vs. 14.7%; $P < 0.001$) and grade 3/4 neutropenia (2.3 vs. 22.8%; $P < 0.001$) resulting in a significantly higher incidence of neutropenic fever and sepsis (0.2 vs. 3.4%, $P < 0.001$), were more frequently observed with 5-FU/LV, whereas grade 3 HFS (17.1 vs. 0.7%) occurred more frequently with capecitabine. Grade 3 hyperbilirubinemia appeared more frequently (18.3 vs. 3.3%; $P < 0.001$) in the capecitabine group but tended to be an isolated phenomenon involving only indirect bilirubin [52]. Recently, a meta-analysis of the medical resource used in one of the trials demonstrated that single-agent capecitabine as monotherapy treatment for advanced, metastatic colorectal cancer, apart from being efficient and more tolerable than 5-FU/LV, also led to substantial reduction in medical resource use [53].

Capecitabine has been also evaluated as first-line treatment in metastatic colorectal cancer patients in combination either with oxaliplatin [46–49] or with irinotecan [42–45] in noncomparative phase II studies. When administered in combination with oxaliplatin (120 mg/m^2 on day 1 [46–49] or 70 mg/m^2 on days 1 and 8), the dose of capecitabine varied between 750 mg/m^2 b.i.d. [46] and 1250 mg/m^2 [47–49] on days 1–14 followed by 7 days rest in 3-week cycle. The ORR ranged between 37.1 and 55% [46,48], which is comparable to that observed with the FOLFOX regimen [54,55]. The most common treatment related to grade 3/4 AEs appeared to be diarrhea (15% [48] and 35% [47]), oxaliplatin-related sensory neuropathy (7% [49] in a study with the lower dose of oxaliplatin to 17% in another study [48]) and nausea/vomiting (5–13% [48,49]). Grade 3 HFS secondary to capecitabine was much more infrequently observed (2–3% [46–49]) in these studies compared with single-agent capecitabine administration. In addition, grade 3/4 neutropenia occurred in 5.7–7% [46–48] of patients. Although no comparative data are available, the incidence is very low compared with that observed with the FOLFOX4 regimen (42–47% [55,56]). The main reasons for discontinuation were diarrhea [49] and sensory neuropathy [46]. In only one study did the initial dose of capecitabine have to be modified from 1000 mg/m^2 b.i.d. to 750 mg/m^2 b.i.d., because of the high incidence (85%) of diarrhea [46]. When administered concurrently with irinotecan, the dose of capecitabine ranged from 1000 mg/m^2 [45] to 1250 mg/m^2 [44] b.i.d. on days 1–14 followed by 1 week rest for 21 days, while irinotecan was delivered at dose 240 mg/m^2 [45] to 300 mg/m^2 [42] on day 1 or 100 mg/m^2 [44] to 150 mg/m^2 [42] on days 1 and 8 in 3-week cycles. In the study conducted by Bajetta *et al.* [42] (capecitabine 1250 mg/m^2 b.i.d. days 1–14 and irinotecan 300 mg/m^2 day 1 or 150 mg/m^2 days 1, 8 in 3-week cycles) initial dose of both agents had to be modified to a lower dose (capecitabine 1000 mg/m^2 b.i.d. and irinotecan 240 mg/m^2 day 1 or 120 mg/m^2 days 1, 8) because of the increased incidence (> 33%) of grade 3/4 diarrhea. Recently, a phase I/II pharmacokinetic study has demonstrated that the maximum tolerated dose of capecitabine is 1000 mg/m^2 b.i.d. days 1–14 every 3 weeks, when concurrently administered with irinotecan in chemonaive colorectal cancer patients. The recommended dose of the latter is 250 mg/m^2 on day 1 [43]. The ORR in all studies ranged from 42% [43] to 49% [45], which is similar to the results previously reported with FOLFIRI [57]. The most common grade 3/4 AEs were diarrhea (19% [43] to 27% [42]), neutropenia (11–12% [42–45]) and nausea/vomiting (10% [45] to 12% [42]). In all studies, the incidence of grade 3 HFS secondary to capecitabine was lower compared with the one experienced with capecitabine alone [43]. Although no comparative trial was performed, grade 3/4 neutropenia occurred less frequently (11–12 vs. 46%) than with FOLFIRI, whereas the incidence of grade 3/4 diarrhea was higher [42,58]. Both capecitabine combinations either with oxaliplatin or with irinotecan revealed comparable efficacy with FOLFOX4 and FOLFIRI, respectively, with acceptable safety and tolerability. The results of ongoing randomized comparative phase III trials will ascertain the future of these combinations in the first-line treatment of colorectal cancer.

In the adjuvant setting, capecitabine has been administered either as monotherapy or in combination with oxaliplatin. In a randomized, multicenter, comparative phase III trial (X-ACT) 1987 Dukes C resected colon cancer patients were randomized to receive as adjuvant treatment either single-agent capecitabine [1250 mg/m^2 b.i.d. days 1–14 every 21 days ($n = 1004$)] or the Mayo Clinic regimen [LV 20 mg/m^2 i.v. followed by bolus i.v. administration of 5-FU, 425 mg/m^2 on days 1–5 every 28 days, ($n = 983$)] over a period of 24 weeks [37]. The X-ACT study demonstrated a significantly superior relapse-free survival ($P = 0.053$) and trends toward superior disease-free survival ($P = 0.053$) and overall survival ($P = 0.071$) for the capecitabine arm. In addition, a positive safety profile was observed with capecitabine, producing significantly less of all grades of diarrhea (46 vs. 64%; $P < 0.001$), nausea/vomiting (36 vs. 51%; $P < 0.001$), stomatitis (22 vs. 60%; $P < 0.001$), alopecia (6 vs. 22%; $P < 0.001$) and neutropenia (32 vs. 63%; $P < 0.001$). In adverse, HFS was more frequently observed (60 vs. 9%; $P < 0.001$) with capecitabine. In

addition, grade 3/4 neutropenia (2 vs. 26%; $P < 0.001$) leading to febrile neutropenia and consequently to sepsis (0.3 vs. 3%; $P < 0.001$), and stomatitis, (2 vs. 14%; $P < 0.001$) were significantly more common in the 5-FU arm. Grade 3 hyperbilirubinemia (≥ 3 times the upper limit of normal) was more common with capecitabine (18 vs. 5.9%). The incidence of grade 3/4 abnormalities of the hepatic enzymes (serum glutamic-oxoacetic transaminase, serum glutamate-pyruvate transaminase), however, was low in both treatment arms (0.7 and 1.6%, respectively, with capecitabine, and 0.3 and 0.6%, respectively, with 5-FU/LV). The safety profile of capecitabine was similar, regardless of patients' age (< 65 or ≥ 65 years of age). The incidence of first and second dose reduction was higher in patients receiving 5-FU/LV (42 and 13%, respectively, for capecitabine, and 44 and 26%, respectively, for the later). In addition, median time to first and second dose reduction was longer with capecitabine, compared with 5-FU/LV (78 and 113 days, respectively, for capecitabine, and 41 and 57 days, respectively, with 5-FU/LV). Premature withdrawal was infrequent in both treatment arms (16 vs. 12%) [50]. These results led the FDA to approve capecitabine as single-agent adjuvant therapy for Dukes C colon cancer patients, when single fluoropyrimidine therapy is preferred [36].

In another randomized phase III trial in Dukes C colon cancer patients, three arms of adjuvant chemotherapy were compared: XELOX (capecitabine at dose 1000 mg/m^2 b.i.d. days 1–14 plus oxaliplatin 130 mg/m^2 on day 1, every 21 days for 8 cycles); Mayo Clinic regimen (LV 20 mg/m^2 i.v. bolus plus 5-FU 425 mg/m^2 i.v. bolus on days 1–5, every 28 days for 6 cycles); and Roswell Park regimen (LV 500 mg/m^2 i.v. plus i.v. 5-FU 500 mg/m^2 on day 1, weeks 1–6, in four 8-week cycles). Early safety data were presented at the American Society of Clinical Oncology 2005 meeting [59]. XELOX compares favorably with the other arms of the study [60]. Grade 3/4 neutropenia (5.3 vs. 14 vs. 3% respectively), febrile neutropenia (0.2 vs. 4.7 vs. 1.7% respectively), and also stomatitis (0.6 vs. 11.2 vs. 0%, respectively) were less frequently observed with XELOX than with other treatment arms. Grade 3 HFS (3.6 vs. 0.2 vs. 0.2%, respectively), sensory neuropathy (8.1 vs. 0 vs. 0%), and vomiting (5 vs. 1.7 vs. 4.6%) occurred more frequently with XELOX compared with the other two arms. The incidence of grade 3/4 diarrhea was approximately the same with XELOX and the Mayo Clinic regimen (15 vs. 13.5%, respectively), but higher with Roswell Park regimen (26.2%). Early safety results of XELOX administration are comparable with those of the FOLFOX regimen, the standard adjuvant therapy for colon cancer patients [60]. Efficacy results will be available in 2008.

The proven efficacy and safety benefits of capecitabine over i.v. 5-FU/LV in the treatment of metastatic [51,52] and early stage colon cancer [37,50] have led to the development of a number of studies evaluating the use of capecitabine in chemoradiation schedules for patients with locally advanced rectal cancer as single agent as well as in combination with oxaliplatin or irinotecan. Although several dosing and schedule protocols of single-agent capecitabine combined with radiotherapy for locally advanced rectal cancer patients have been evaluated in several noncomparative phase II trials [58,61–65], the continuous administration of capecitabine at a dose of 825 mg/m^2 b.i.d. concurrently with radiotherapy was the most applied [66]. It appears to be tolerable, with no reported grade 4 AEs in most studies, and low incidence of grade 3 toxicities. Additionally, it is more convenient that protracted infusion of 5-FU and demonstrates comparable efficacy achieving satisfactory tumor downstaging rates and pathological response rates [58,61–65] (Table 2). The same observation was made for concurrent administration of XELOX and XELIRI with radiotherapy [67–72] (Table 3). In light of the encouraging results, two large randomized phase III trials are in progress. The National Surgical Adjuvant Breast and Bowel Project R-04 trial is recruiting patients to receive either radiotherapy plus capecitabine ± oxaliplatin or plus infusional 5-FU ± oxaliplatin. Following surgery, patients will be

Table 2 Phase II/III studies of capecitabine chemoradiation regimens in patients with LARC

Study	Number of patients	Treatment	Downstaging rate (%)	Pathological complete response rate (%)	Main 3/4 adverse events
Krishnan *et al.* [64]	51	(52.5 Gy/30 fractions) primary tumor + perirectal nodes + capecitabine (850 mg/m^2 b.i.d.)	52	18	Grade 3/4 dermatitis (9%), grade 3/4 diarrhea (2%)
Kim *et al.* [65]	95	Pelvic RT (46 Gy) + 4 Gy boost × 5 weeks + capecitabine (825 mg/m^2 b.i.d.)	76	12	Grade 3 diarrhea (3%), neutropenia (1%). No grade 4 toxicities
Dunst *et al.* [61]	63	Pelvic RT (1.8 Gy/day) + presacral boost (3 × 1.8 Gy) + capecitabine (825 mg/m^2 b.i.d.) × 6 weeks	73	4	Grade 3 leukopenia (10%), diarrhea (4%). No grade 4 toxicities
Lin *et al.* [62]	52	Pelvic RT (45 Gy) + primary tumor/perirectal node RT (52.5 Gy) + capecitabine (825 mg/m^2 b.i.d.) × 5 weeks	62	17	Grade 3 diarrhea (13%), radiation dermatitis (6%). No grade 4 toxicities

b.i.d., twice daily; LARC, locally advanced rectal cancer; RT, radiotherapy.

administered FOLFOX ± bevacizumab. The Pan-European Trials in Adjuvant Colorectal Cancer 6 trial compares neoadjuvant capecitabine plus radiation followed by adjuvant capecitabine with or without oxaliplatin.

Breast cancer

Either as first-line chemotherapy or in pretreated patients with advanced and metastatic breast cancer, capecitabine has been evaluated as a single agent and in combination with other chemotherapeutic agents, most often with a taxane.

In the monotherapy setting of metastatic breast cancer, most studies of capecitabine have been conducted primarily among patients previously treated with an anthracycline and/or a taxane [73–78] (Table 4). Such patients have very poor prognosis. Even when salvage chemotherapy with infusion 5-FU combined with high-dose LV and cyclophosphamide is applied, the 1- and 2-year survival rate does not exceed 51 and 20%, respectively [79]. Most studies were phase II/III trials and patients received the standard dose of single-agent capecitabine, 1250 mg/ m^2 b.i.d., for 2 weeks followed by a 1-week rest for 21 days. Down-dosing of capecitabine was frequent and in one study a 25% dose reduction in half the study population was reported [77]. Capecitabine proved to be effective, yielding ORR from 15% [75] to 36% [73], and stable disease (SD) rates from 23% [73] to 46% [75]. Median time to disease progression varied from 3 months [73] to 5.9 months [76], whereas median overall survival ranged from 7.6 months [73] to 15.2 months [76]. The most frequently observed grade 3 (or 4) nonhematologic AEs were HFS (range 9% [73] to 42% [74]), diarrhea (range 0% [73] to 30% [74]), nausea (range 3% [75] to 35% [78]), and vomiting 6% [73] to 19% [74]). In all studies, capecitabine therapy appeared to be associated with low incidence of grade 3 or 4 neutropenia, ranging from 0% [75] to 9% [73]. In one multicenter randomized phase II study, patients with anthracycline-pretreated breast cancer were randomized to receive either capecitabine (1255 mg/m^2 b.i.d. 2 weeks on/1 week off in 3-week cycles, for 2 cycles) or paclitaxel (175 mg/m^2 every 3 weeks) [73]. ORR was greater in the capecitabine arm (36 vs. 26%, $P = 0.52$) but not significant. Tolerability profiles were different with more all-grade diarrhea (41 vs. 16%), vomiting (41 vs. 16%),

Table 3 **Early clinical studies of capecitabine–oxaliplatin and capecitabine–irinotecan chemoradiation regimens in patients with LARC**

Study	Number of patients	Treatment	Downstaging rate (%)	Pathological complete response rate (%)	Grade 3/4 adverse events
Rödel *et al.* [69]	32	Pelvic RT (total dose 50.4 Gy) + capecitabine (825 mg/m^2 days 1–14, 22–35) + oxaliplatin (50 mg/m^2 day 1, 8, 22, 29)	55	19	Grade 3: diarrhea (6), skin reactions (6)
Machiels *et al.* [67,70]	40	Pelvic RT (total dose 45 Gy) + capecitabine (825 mg/m^2 b.i.d. 5 days/week × 5 weeks) + oxaliplatin (50 mg/m^2 day 1, 8, 15, 22, 29)	58	14	Grade 3/4 diarrhea (30)
Rodel *et al.* [68]	104	Pelvic RT (total dose 50.4 Gy) + capecitabine (825 mg/m^2 days 1–14, 22–35) + oxaliplatin (50 mg/m^2 day 1, 8, 22, 29)	50	17	Grade 3/4 sensory neuropathy (18), diarrhea (12)
Willeke *et al.* [71]	30	Pelvic RT (total dose 50.4 Gy) + capecitabine (500 mg/m^2 b.i.d., days 1–38) + irinotecan (50 mg/m^2 day 1, 8, 15, 22, 29, 36)	Not reached	18	Grade 3/4 leukopenia (20), grade 3 nausea/vomiting (3), grade 3 transaminase increase (3)
Gollins *et al.* [72]	22	Pelvic RT (total dose 45 Gy) + capecitabine (650 or 850 mg/m^2 b.i.d.) + irinotecan (50–70 mg/m^2/week) × 5 weeks	74	26	Grade 3 diarrhea (9), anorexia (9), nausea/vomiting (5), lethargy (5). No grade 4 adverse events

b.i.d., twice daily; LARC, locally advanced rectal cancer; RT, radiotherapy.

Table 4 **Efficacy and safety data of single-agent capecitabine in pretreated metastatic breast cancer patients**

Study	Previous treatment	Initial regimen of capecitabine	Number of patients	Objective response rate (%)	Main 3/4 adverse events (%)
Wist *et al.* [78]	Anthracyclines, taxanes	1.250 mg/m^2 b.i.d. days 1–14 q3w	48	29	HFS (35), nausea (35). No grade 3/4 hemtologic adverse events
Fumoleau *et al.* [76]	Anthracyclines, taxanes	1.250 mg/m^2 b.i.d. days 1–14 q3w	126	28	HFS (21), diarrhea (10), neutropenia (6)
Reichardt *et al.* [75]	Anthracyclines, taxanes	1.250 mg/m^2 b.i.d. days 1–14 q3w	136	15	HFS (13), diarrhea (8), nausea (3), neutropenia (0)
Talbot *et al.* [73]	Anthracyclines	1.255 mg/m^2 b.i.d. days 1–14 q3w	22	36	HFS (9), diarrhea (0), nausea (9), vomiting (9), neutropenia (9)
Blum *et al.* [77]	Taxanes	1.255 mg/m^2 b.i.d. days 1–14 q3w	74	31	HFS (22), diarrhea (19), nausea (10), vomiting (6), neutropenia (1)
Blum *et al.* [74]	Paclitaxel, anthracycline	1.255 mg/m^2 b.i.d. days 1–14 q3w	135	20	HFS (42), diarrhea (30), nausea (27), vomiting (19), neutropenia (3)

b.i.d., twice daily; HFS, hand–foot syndrome.

and HFS (18 vs. 0%) in the capecitabine group, and a higher incidence of all-grade alopecia (47 vs. 0%) and musculoskeletal effects (26 vs. 0%) in the paclitaxel arm. The overall incidence of grade 3/4 AEs were lower, but not statistically significant (36 vs. 68%, $P = 0.6$) in the capecitabine arm. In addition, grade 3 leukopenia (0 vs. 21%, $P = 0.038$) and grade 3 neutropenia (9 vs. 53%) were significantly less frequent with capecitabine compared with paclitaxel [73].

In light of the promising findings in pretreated metastatic breast cancer patients, capecitabine is being investigated as single-agent first-line treatment of breast cancer, especially in elderly patients. In a randomized controlled phase II trial, women more than 55 years of age were administered three cycles either of capecitabine, 1255 mg/m^2 b.i.d. for 14 days with 7 days rest for 21 days ($n = 61$) or cyclophosphamide with methotrexate and 5-FU (CMF) ($n = 32$) [80]. ORR, median TTP (4.1 vs. 3.0 months), and median overall survival (19.6 vs. 17.2 months) were greater in the capecitabine arm compared with the CMF group (30 vs. 16%, $P = 0.21$), but not statistically significant. Adverse effect profile was different, with higher incidence of all-grade HFS (43 vs. 0%; $P < 0.001$) and diarrhea (47 vs. 22%; $P = 0.02$) in the capecitabine arm, and lower incidence of hematologic AEs. Grade 3/4 neutropenia (8 vs. 41%; $P = 0.005$) and grade 4 neutropenia (2 vs. 22%; $P = 0.002$) leading to sepsis were observed significantly less frequently in patients receiving capecitabine [80]. More recently, 73 patients ≥ 65 years of age received as first-line treatment capecitabine at dose either 1250 mg/m^2 b.i.d. 2 weeks on/1 week off for 21 days ($n = 30$) or 1000 mg/m^2 b.i.d. with the same schedule ($n = 43$) [81]. Although the activity was similar in both cohorts with ORR being 35 vs. 37%, respectively, the low-dose cohort appeared to achieve a greater median time to survival (16 vs. 10 months) with a lower incidence of grade 3/4 diarrhea (2 vs. 13%), nausea (5 vs. 7%), dyspnea (5 vs. 10%), and vomiting (0 vs. 3%). The incidence of grade 3 HFS was indifferent between the two cohorts [81].

In the combination treatment setting, capecitabine, concurrently administered with a wide range of cytotoxic and biologic agents, including among others taxanes, vinorelbine, bevacizumab, and trastuzumab has been investigated.

In an international randomized phase III trial, 511 anthracycline-pretreated breast cancer patients received six cycles of either single-agent docetaxel at dose 100 mg/m^2 on day 1 in a 3-week cycle or capecitabine at dose 1250 mg/m^2 b.i.d. day 1–14 followed by 1 week rest in a 3-week cycle plus i.v. docetaxel at a dose of 75 mg/m^2 on day 1 of each cycle [82]. ORR was significantly higher in the combination arm compared with the docetaxel group (42 vs. 30%, $P = 0.006$), whereas the former demonstrated significantly superior TTP (6.1 vs. 4.2 months, $P = 0.001$) and significantly superior median overall survival (14.5 vs. 11.5 months; $P = 0.0126$). In addition, the safety profile of the combination therapy arm was more manageable with less-frequent all-grade AEs (25 vs. 31% respectively). Nonhematologic grade 3/4 AEs, such as stomatitis (17.4 vs. 5%), diarrhea (14.4 vs. 5.4%), nausea (6 vs. 2%), and grade 3 HFS (24 vs. 1%) were more common in patients receiving the combination therapy, whereas grade 3/4 neutropenic fever was observed more frequently (16 vs. 21%) in the docetaxel group. Dose reduction was required in 51% of patients for the combination group and in 36% of patients for the docetaxel arm, without negative impact on efficacy [20]. The same combination regimen was evaluated as neoadjuvant treatment in stages II and III breast cancer patients in a randomized phase III study [83]. Overall, 204 patients were randomized to receive four cycles either of capecitabine plus docetaxel (XT) (capecitabine at dose 1000 mg/m^2 b.i.d. 2 weeks on/1 week off for 21 days plus docetaxel 75 mg/m^2 on day 1) or the standard AC therapy (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, both on day 1 in a 3-week cycle) [83]. Analysis revealed that capecitabine plus paclitaxel was more effective than AC, resulting in significantly higher ORR (84 vs. 67%, $P = 0.0047$). In terms of grade 3/4 AEs, HFS (22 vs. 0%) and stomatitis (10 vs. 0%) were more frequently observed in the capecitabine plus paclitaxel group, whereas grade 3/4 neutropenia (72 vs. 85%) was more common in the AC arm [83].

Capecitabine plus paclitaxel in anthracycline-pretreated metastatic breast cancer patients was evaluated in two studies with different dose and schedule settings. Blum *et al.* [84] administered capecitabine at a dose of 850 mg/m^2 day 1–14 for 21 days plus weekly i.v. paclitaxel at dose 80 mg/m^2 day 1, 8 in 55 metastatic breast cancer patients, whereas in the other study 72 metastatic breast cancer patients received capecitabine at a dose of 1000 mg/m^2 b.i.d. on days 1–14 for 21 days plus paclitaxel intravenously at a dose of 175 mg/m^2 on day 1 [85]. In both studies, combination treatment demonstrated high activity, achieving comparable ORR (50 vs. 52%, respectively). The most common grade 3/4 AEs with the 3-weekly schedule were alopecia (22%), neutropenia (12%), and HFS (11%) [85], whereas the most common grade 3/4 AEs with the weekly schedule were HFS (18%), neutropenia (12%) and diarrhea (5%) [84]. Both regimens merit further evaluation as first-line treatment for women with MBC in randomized phase III trials.

Capecitabine plus i.v. vinorelbine has shown high activity in anthracycline and/or taxane-pretreated metastatic breast cancer patients. In three phase II studies, capecitabine plus i.v. vinorelbine achieved an ORR of 50–70% [86–88]. This combination, apart from being effective, was well tolerated. Minimal nonhematologic

grade 3/4 AEs were reported. The most common treatment-related grade 3/4 AE was neutropenia ranging from 13.3% [86] to 39% [89]. Actually, completely oral combinations of both drugs are under evaluation [89].

Capecitabine-based chemotherapy in combination with biologic agents, either bevacizumab or trastuzumab, was evaluated in metastatic breast cancer patients. In a phase III trial, 462 anthracycline and taxane-pretreated metastatic breast cancer patients were randomized to receive either single-agent capecitabine at a dose of 1250 mg/m^2 b.i.d. days 1–14 every 3 weeks or in combination with bevacizumab at a dose of 15 mg/kg on day 1 [90]. Although ORR was significantly superior with the combination arm (19.8 vs. 9.1%, $P = 0.001$) progression-free survival (4.86 vs. 4.17 months) and overall survival (15.1 vs. 14.5 months respectively) of both arms were comparable. The incidence of all-grade AEs did not differ between the two groups. Only grade 3/4 hypertension (17.9 vs. 0%, $P < 0.001$) was significantly more common in the combination arm [90]. In addition, capecitabine combined with trastuzumab in HER-2-positive metastatic breast cancer patients showed high activity with satisfactory tolerability as first-line treatment and in pretreated patients. In the first-line setting the reported ORR was 73%, whereas no grade four AEs were observed. Only four patients experienced grade 3 HFS and one patient experienced grade 3 leukopenia [91]. In pretreated patients, ORR ranged between 41% [92] and 52% [93] whereas median TTP was 5.2 and 6.4 months, respectively. Yamamoto *et al.* [92] did not report any grade 3/4 AEs. In the second study 8 and 4% of patients experienced anemia and leukopenia, respectively [93]. Grade 3/4 nonhematologic AEs were minimal. An open-label, randomized phase II study evaluating the triple combination of docetaxel with capecitabine and trastuzumab vs. docetaxel with trastuzumab is ongoing. Preliminary safety data reveal a favorable safety profile of the triple combination [94].

In the elderly population

The efficacy, safety, and tolerability of capecitabine in an elderly population is an important issue as many patients receiving the drug, including those with colon and breast cancer, are more than 65 years of age. Although there are few specific data available for this subpopulation of patients, results from published clinical studies suggest that capecitabine is both safe and efficient in older patients with breast and colon cancer.

In an elderly breast cancer population, capecitabine was used in the metastatic setting. As first-line treatment it was administered primarily as a single agent (1250 mg/m^2 b.i.d. for 14 days followed by 7 days rest) and in combination with vinorelbine (capecitabine 750–1250 mg/m^2 b.i.d. in the same 3-week cycle plus vinorelbine at 20–45 mg/m^2 per day on days 1–3). As second-line therapy, capecitabine was used only as monotherapy at a dose of 1000 mg/m^2 b.i.d. in the same 3-week cycle [80,95–97].

Capecitabine either as first-line monotherapy or as combination therapy has proven to be effective, achieving ORR ranging from 27 to 55%, and SD rates from 18 to 51%. In the second-line setting, capecitabine has also been active (ORR 28–36%, SD 32–44%) [98,99]. In addition, it proved to be safe and well tolerated, especially when administered at a dose ranging from 850 to 1000 mg/m^2 b.i.d. The incidence of grade 3/4 neutropenia was low, ranging from 0 to 8% [36,96], whereas the most common nonhematologic AEs were HFS (2–24%), diarrhea (3–10%), stomatitis (3–8%), mucositis (3–7%), and nausea/vomiting (3–7%) [80,95–97].

In colorectal cancer population, capecitabine was initially administered as first-line treatment either as single agent (1250 mg/m^2 b.i.d. 2 weeks on/1 week off, later with down-dosing at 1000 mg/m^2 b.i.d.) [6,52,100,101] or in combination with oxaliplatin (85–130 mg/m^2 on day 1) [102–104], and with irinotecan (60 mg/m^2 on days 1, 8 and 15) [105]. In the adjuvant setting, capecitabine was delivered in the X-ACT study as monotherapy (1250 mg/m^2 b.i.d. 2 weeks on/1 week off) compared with the Mayo Clinic regimen (bolus 5-FU 425 mg/m^2 with LV 20 mg/m^2 days 1–5 every 4 weeks).

As first-line treatment, capecitabine either as monotherapy or in combination with oxaliplatin was shown to be more active than the Mayo Clinic regimen. The ORR as monotherapy ranged from 12 to 24% [100,106], whereas as combination therapy it varied from 32 to 52% [102,104,105]. In a randomized controlled study comparing capecitabine monotherapy with the Mayo Clinic regimen in patients more than 60 years [6], the ORR was significantly greater with capecitabine (26 vs. 16%, $P = 0.018$) and it did not differ between those more than 60 years of age and those 60 years of age or younger (26 vs. 24%, $P = 0.688$). In addition, its safety profile was acceptable and comparable with that of younger patients [6]. Across studies, grade 3/4 hematologic AEs were infrequent, regardless of regimen. Neutropenia and thrombocytopenia occurred in less than 10% of patients, whereas there was no record of neutropenic fever. Among the nonhematologic grade 3/4 AEs, diarrhea (range 0–18%), nausea/vomiting (0–14%), paresthesia (range 0–18%), and grade 3 HFS (range 0–21%) were the most frequently observed [101,103]. Grade 3 HFS occurred more often with single-agent capecitabine administration (range 0–21%) than with capecitabine combination regimens (0–6%) [48,102–104], whereas grade 3/4 diarrhea was more common with combination regimens [100–102,104]. In the adjuvant setting the capecitabine monotherapy arm, especially in patients with Dukes C colon cancer, revealed significantly superior relapse-free

survival ($P = 0.041$) and trends toward superior disease-free survival ($P = 0.053$), and overall survival ($P = 0.071$) [107]. With regard to the safety profile, elderly patients treated with capecitabine experienced significantly less frequently grade 3/4 neutropenia compared with those treated with 5-FU/LV. Nonhematologic AEs were significantly lower in incidence (diarrhea 52 vs. 68%, $P = 0.002$; nausea 33 vs. 47%, $P = 0.005$; stomatitis 23 vs. 67%, $P < 0.001$) in the capecitabine group, except all-grade HFS, which was observed significantly more frequently with capecitabine compared with 5-FU/LV (63 vs. 81%, $P < 0.0001$) [107].

Management of adverse events

Appropriate patient selection, according to contraindications and special precautions, is important in defining the population most likely to benefit from capecitabine treatment without compromising tolerability.

Dose adjustments with grade of toxicity

Dosage adjustments based on tolerability are recommended. Grade 1 toxicity does not necessitate dosage reduction. For toxicities of grade 2 or higher, modifications, however, are recommended. Capecitabine should be discontinued until symptoms subside to grade 1 or less. It can be reintroduced at 50 or 100% of the initial dose, depending on the severity and frequency of the adverse effects. Only for grade 4 toxicity should discontinuation of the treatment be considered or if the clinician decides that treatment is beneficial for the patient, interruption is recommended until toxicity resolves to grade 0/1. Re-administration at half the initial dose is recommended (Table 5) [12].

Table 5 Dose adjustment scheme for patients receiving capecitabine single-agent therapy

Adverse event grade	During therapy	Dose reduction for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interrupt until resolved to grade 0/1	Maintain dose level
Second appearance	Interrupt until resolved to grade 0/1	25%
Third appearance	Interrupt until resolved to grade 0/1	50%
Fourth appearance	Discontinue treatment permanently	
Grade 3		
First appearance	Interrupt until resolved to grade 0/1	25%
Second appearance	Interrupt until resolved to grade 0/1	50%
Third appearance	Discontinue treatment permanently	
Grade 4		
First appearance	Discontinue treatment permanently OR Interrupt until resolved to grade 0/1 if the clinician deems it to be in the patient's best interest to continue therapy	50%

Dose adjustments according to age

Although there are few specific data published concerning capecitabine administration in elderly patients – more than 65 years of age – preliminary results have revealed its efficacy, safety, and tolerability in that subpopulation of patients. Therefore, no dose adjustments according to age are recommended, but caution should be exercised as renal impairment is common in these patients [12,108].

Safety and efficacy of capecitabine administration in adolescent patients – less than 18 years of age – has not yet been established, although studies in that age group are ongoing. Pending the preliminary results, its administration should be avoided [12].

Contraindications

Renal dysfunction

Although renal impairment has no effect on the pharmacokinetic of capecitabine or 5-FU, it leads to a significant increase in systemic exposure to 5′-DFUR and sequentially to increased frequency of capecitabine-related AEs [15]. Therefore, capecitabine is contraindicated in patients suffering from severe renal failure (ClCr < 30 ml/min). The dose of the drug in patients with moderate kidney dysfunction (ClCr 30–50 ml/min) should be 75% of the normal full dose. Patients with mild kidney dysfunction (ClCr > 50 ml/min) can receive the full dosage, but with close monitoring during treatment. Treatment-related toxicity can be unpredictable due to altered drug clearance, and bilirubin exceeding 5 mg/dl is generally considered an absolute contraindication for the administration of cytotoxic agents. The pharmacokinetics of capecitabine are not affected in patients with mild to moderate hepatic dysfunction, and limited data suggests that capecitabine can be safely administered without dose adjustment in patients with extensive liver metastases and hepatic dysfunction [39]. Table 6 provides the contraindications of capecitabine [15,39].

Table 6 Contraindications of capecitabine

Deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)
Severe kidney dysfunction
Severe leukopenia, neutropenia, or thrombocytopenia
Severe liver impairment
Severe reaction to fluoropyrimidine therapy
Pregnancy
Lactation
Use of antiviral sorivudine or brivudine, blockers of DPD enzyme

Malabsorption

Physical abnormality of the upper gastrointestinal tract or malabsorption syndrome may also adversely affect the

absorption of capecitabine. As a result, its administration is not recommended in patients with these conditions [12].

Capecitabine and dihydropyrimidine dehydrogenase deficiency

Capecitabine is also not recommended in patients with DPD deficiency. There have been reports in patients with DPD deficiency treated with capecitabine, in whom the toxicity profile was very severe [109]. DPD is the rate-limiting enzyme in 5-FU catabolism, mediating the conversion of 5-FU to 5-dihydrofluorouracil with subsequent catabolism by dihydropyrimidase and β-ureidopropionase enzymes to ultimately produce FBAL, ammonia, and CO_2 [110]. In humans, 80–90% of the administered dose of 5-FU is degraded by DPD [110]. DPD deficiency secondary to 5-FU or to capecitabine administration is an autosomal co-dominantly inherited pharmacogenetic syndrome because of genetic alterations of the DPD gene, with a variable phenotype that ranges from partial to complete loss of DPD enzyme activity resulting in excessive amounts of 5-FU available for anabolization to its active metabolites [111]. The most prominent mutation is the IVS 14 + 1G→A, in the splicing donor consensus sequence of intron 14, resulting in a truncated protein [112]. The prevalence of DPD deficiency in the general population is about 3–5% [113]. In cases of unexpected severe toxicity during capecitabine treatment, DPD deficiency should be considered. Syndrome of DPD deficiency manifests as diarrhea, stomatitis, mucositis, neurotoxicity, and, in some cases, death. Symptoms are unrecognizable until exposure to the drug [114]. Potential screening tests with oral uracil breath tests, which have proved to be very accurate for the assessment of DPD activity with 96% specificity and 100% sensitivity [111,115], may facilitate the detection of DPD deficiency and contribute to the identification of cancer patients at risk for severe toxic side effects before 5-FU and capecitabine administration [109].

Others

The drug is not recommended in patients with any psychiatric disorder or condition rendering them incapable of understanding or complying with the healthcare provider's instructions. Patients with central or peripheral neuropathy, hypocalcemia or hypercalcemia, diabetes or electrolyte disturbances should be monitored very carefully during capecitabine treatment [12].

Specific adverse events and their management

Hand–foot syndrome

HFS is a cutaneous adverse effect also referred to as palmar–plantar erythrodysesthesia or chemotherapy-induced acral erythema. It is the most common adverse effect associated with capecitabine and has a median time to onset of 79 days but can also range from 11 to 360 days. Although the exact mechanism is unknown, there are three leading hypotheses. According to the first hypothesis, skin keratinocytes might have upgraded levels of the enzyme DPD, resulting in capecitabine's metabolite accumulation, and hence an increased likelihood of developing HFS [116]. The second hypothesis is that capecitabine may be eliminated by the ecrine system; therefore, HFS is caused by an undefined mechanism relating to the increased number of ecrine glands on the hands and feet [117]. Finally, increased vascularization and increased pressure and temperature in the hands and feet may lead to HFS manifestation. Several systems of HFS classification are present. A general three-grade classification from the National Cancer Institute, a four-grade from World Health Organization, and a practical three-grade one that was used in clinical trials of capecitabine [118]. According to the latter, grade 1 is defined as the presence of numbness, tingling, painless swelling, dysesthesia, paresthesia, erythema or discomfort of the hands and/or feet. Grade 2 is characterized by a painful erythema, and swelling of the hands or feet, but does not interfere with the patient's daily living activities. Grade 3 involves the presence of skin blistering, ulceration, desquamation or severe pain in the hands and/or feet, which prevents the patient from working or performing activities of daily living [118]. In patients with DPD enzyme deficiency a variant of HFS was reported, where only the palms of both hands and soles of both feet were tender with no apparent rash or discoloration [119].

Dose interruption followed, if necessary, by dose reduction as recommended by the guidelines for the general management of any AE during capecitabine administration and as enclosed in the package insert (Tables 5 and 6) should be the mainstay of HFS management. If guidelines are followed, rapid reversal of signs and symptoms without long-term consequences is observed. HFS syndrome rarely requires hospital admission. Apart from dose interruption and/or reduction, there are few effective supportive measures. Prophylactic and symptomatic treatment of grade 1 HFS appears to be the administration of pyridoxine (vitamin B_6) [119,120]. The use of pyridoxine at a highly variable dose, 50–150 mg three times a day for 6 weeks, may improve the palmar–plantar erythrodysesthesia associated with capecitabine, as anecdotally reported by a few clinical studies [121,122]. As pyridoxine is a safe nutritional supplement, its prophylactic use seems to be appealing, but its effectiveness needs to be proven in controlled studies before being recommended as routine treatment. Prophylactic use of celebrex is not recommended, although its concurrent administration in a retrospective study of 67 patients receiving capecitabine appeared to reduce the incidence of HFS > grade 1 (from 34% with capecitabine alone to 13% with concurrent celebrex administration) [123]. Further evaluation of this hypothesis is needed.

Topical and systemic corticosteroids have been reported to be effective in the treatment of HFS secondary to other agents [124,125], but their long-term administration may lead to skin thinning, which may worsen the symptoms. As there are no data available for capecitabine-related HFS, their use is unproven [12]. Nicotine patches have been anecdotally demonstrated to relieve capecitabine-related HFS symptoms [126]. Their use is not recommended [12] because of lack of randomized controlled studies. Good skin and nail care and avoidance of extreme temperatures, pressure and friction of the skin, however, are thought to be useful in preventing the worsening of symptoms but are no substitutes for dose interruption and, if necessary, dose modification.

Cardiotoxicity

A serious, but rare, toxic adverse effect is cardiac toxicity. It has been reported in 1.5–18% of patients treated with 5-FU [127,128]. A recent retrospective analysis of 596 patients with metastatic colon cancer receiving capecitabine monotherapy as first-line treatment and of 236 patients with taxane-pretreated metastatic breast cancer receiving capecitabine monotherapy showed a lower incidence (3%) of capecitabine-related cardiotoxic events of all grades [129]. The etiology of capecitabine and 5-FU-induced cardiotoxicity is believed to be common but still not well defined. It is proposed to be secondary to myocardial ischemia, which is supposedly induced by coronary vasospasm [130]. The most common symptom is angina-like chest pain. Patients may also experience cardiac arrhythmias (tachycardia, bradycardia, atrial fibrillation, and ventricular extrasystole), myocarditis, congestive heart failure, dilatated cardiomyopathy, cardiogenic shock, cardiac arrest or sudden death syndrome. The incidence of such events is more common when cardiac and/or renal comorbidity are present. Although this is not an absolute contraindication for the administration of capecitabine, dose reduction either alone or in addition to prophylactic antianginal medication and close monitoring may be required for the possibility of any cardiac abnormalities during therapy [131]. A history of previous cardiotoxicity associated with 5-FU should be regarded as a contraindication and such patients should not be re-challenged [12].

Gastrointestinal toxicity

Gastrointestinal symptoms may include nausea, vomiting, diarrhea, abdominal pain, anorexia, stomatitis, constipation, ileus, and dyspepsia. Diarrhea (with or without abdominal cramp) is the most common and dangerous side effect associated with capecitabine, although more frequently observed in colon cancer patients receiving i.v. 5-FU/LV [52]. It is believed that intestinal conversion of capecitabine to 5′-DFCR, by the intestinal CES2 carboxylesterase isoenzyme, is responsible for this side effect. The exact mechanism, however, is not yet clarified [132]. Abdominal pain can precede the onset of diarrhea. Patients more than 80 years of age are particularly susceptible to these symptoms and, therefore, close monitoring is recommended [133]. Any episode of diarrhea that lasts for over 24 h after drug discontinuation is of particular concern. The greatest danger results from patients underestimating the severity of the condition, not reporting it to their doctor and continuing to take the drug. Diarrhea can be treated with loperamide and oral or i.v. rehydration and electrolyte replacement as well as avoiding certain foods [134]. Loperamide may not only reduce diarrhea through its anticholinergic properties but also by inhibiting intestinal CES2 hydrolysis of capecitabine and sequentially reducing the local concentrations of 5′-DFCR [132]. A small proportion of patients may require treatment with oral antimicrobials (fluoroquinolones) [133]. When diarrhea is coupled with neutropenic fever, hospital admission ought to be considered. No patients treated with capecitabine have required octreotide so far. Constipation, although rare, can be managed by increasing liquid, vegetable, and fruit intake. All patients administered capecitabine should be encouraged to drink abundantly (>2 l/day) [12]. Stomatitis, a nonspecific capecitabine-related AE, is not common. Symptoms of grade 1 stomatitis can be controlled with the use of mouthwash with salt or baking soda (1 teaspoon per 250 ml water). Prophylactic avoidance of spicy foods and acidic fruits may be beneficial. For grade 2 stomatitis, oral antiseptics, such as chlorexidine, and anti-inflammatory agents such as benzydamine are recommended [134]. Fewer patients with grade 3/4 stomatitis will require local treatment with fluconazole oral gels. In addition, patients receiving the drug are less likely to require 5-HT_3-antagonist antiemetics (e.g. granisetron, ondasetron). Therefore, nausea and vomiting can be treated with a single agent such as a low-dose corticosteroid (Multinational Association of Supportive Care in Cancer – Antiemetics Guidelines 2004) or metoclopramide/alizapride. Anorexia is uncommon, but it could be controlled by recommending patients to eat frequent, small, tasty meals, chilled food with carbonated drinks, and even spicy foods when stomatitis is not present. Dyspepsia can be managed by the use of antacids or H2-antagonists [135], other than cimetidine. The latter is speculated to interfere with capecitabine administration [12] although specific data are not available. Antacids, others than Maalox, should be given 2 h before or after capecitabine administration to avoid potential interference with absorption, although their effect has not been studied. Maalox, even when delivered concomitantly, has no effect on capecitabine absorption. Therefore no dose or time adjustment is needed when simultaneously delivered with capecitabine [135].

Others

Our group noticed hypokalemia in 20% of patients on capecitabine without any obvious etiology. Since regulation

of potassium homeostasis depends on normal renal function, it is postulated that hypokalemia may be related to the effect of capecitabine on renal tubules [136]. Due to potential complications, hypokalemia in patients on capecitabine deserves special diagnostic and therapeutic attentions. Further analysis to characterize the mechanism is needed.

Other possible treatment-related symptoms are dry or itchy skin (which can be prevented by the use of hydrating creams), tiredness, weakness, dizziness, headaches, fever, pain, sleeplessness, and a decrease in libido [133]. Alopecia, although rare, may need cosmetic support (wigs, etc).

Patient education

It is important that the clinician educate patients on how to use the drug correctly (dosage, length of treatment, etc.) and how to recognize any adverse effects. It has to be emphasized that the 1-week break during treatment needs to be observed, because continuous capecitabine intake under the wrong impression that this would be more effective may become harmful for patients' health. Medication should be administered at the recommended time schedule and missed doses must not be doubled. Patients should be trained to recognize the main capecitabine-related AEs and encouraged to contact the supervising clinician. Side effects are generally manageable, but without prompt intervention they could occasionally progress to more severe events.

Discussion

Capecitabine (Xeloda) is an oral fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumor tissue through exploitation of high intratumoral concentrations of TP, an enzyme present at significantly increased concentrations in a wide range of tumor types, including colorectal, breast and gastric cancers, compared with normal tissue. Human pharmacokinetic studies have shown that after oral administration, capecitabine is rapidly and almost completely absorbed through the gastrointestinal wall, thus avoiding direct intestinal exposure to 5-FU. Capecitabine is then metabolized to 5-FU via a three-step enzymatic cascade, with the final stage of this conversion mediated by TP. In a second three-step sequence, 5-FU is catabolized to dihydrofluorouracil by the enzyme DPD and then to fluoro-β-ureidopropionic acid and FBAL, none of which have any antiproliferative activity. Capecitabine is approved for the first-line treatment of patients with metastatic colorectal cancer and adjuvant use in colorectal cancer. It is used in combination with docetaxel for the treatment of patients with metastatic breast cancer after failure of earlier anthracycline-containing chemotherapy and as monotherapy for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and anthracycline-containing therapy or resistant to both paclitaxel but with contraindications to anthracycline therapy.

More recent studies are suggesting that XELOX is an effective and safe regimen when compared with FOLFOX in colon cancer. Noninferiority studies have also shown the activity of capecitabine in gastric and esophageal malignancies. Combinations with targeted agents, such as bevacizumab in colon cancer are underway, whereas the combination with lapatinib is soon to be approved by FDA for breast cancer. Similarly, the update on Cunningham's study of capecitabine plus gemcitabine is anxiously awaited.

The most common side effects associated with capecitabine include diarrhea, nausea, vomiting, stomatitis, abdominal pain, HFS, and fatigue. A low incidence exists of myelosuppression and alopecia. Efforts to manage HFS, such as clinical trials using nicotine patch, are also being made.

A major challenge in the administration of capecitabine is poor tolerance in the US population compared with European patients (Table 7). Haller *et al.* [137] presented data (first-line metastatic colorectal cancer: 5-FU/LV or capecitabine; adjuvant setting: 5-FU/LV or CAPOX) at the Annual Meeting of the American Society of Clinical Oncology (2006) showing more treatment-related toxicity being reported in the US compared with the rest of the world. A gradient of fluoropyrimidine toxicity is observed: US = high, East Asia = low. On account of this poor tolerance, most European trials evaluated capecitabine at a dose of 1250 mg/m^2 b.i.d. (d1–14, q3w). On the other hand, in US trials, capecitabine doses of 1250 mg/m^2 b.i.d.

Table 7 Toxicity comparison in US and non-US population

Treatment-related AE	First-line MCRC: US vs. non-US		Adjuvant CRC: US vs. non-US	
	Adjusted relative risk	*P* value	Adjusted relative risk	*P* value
Grade 3/4	1.77	<0.001	1.47	0.012
Grade 4	1.72	0.094	2.12	0.009
Grade 3/4 GI	1.72	<0.001	1.60	0.003
Serious	1.20	0.291	1.43	0.053
Grade 3/4 neutropenia	1.51	0.044	1.46	0.110
Grade 3/4 laboratory neutrophils	1.20	0.417	1.47	0.118
Dose reductions	1.72	<0.001	1.21	0.193
Discontinuations	1.83	<0.001	2.09	<0.001

AE, adverse event; CRC, colorectal cancer; GI, gastrointestinal; MCRC, metastatic colorectal cancer.

Table 8 Capecitabine dosing schedules

Reference	Trial/regimen	Dose	Schedule
Hochster ASCO, 2005	TREE-1	1000 mg/m^2	b.i.d. d1–14 q3w
Hochster ASCO GI, 2006	TREE-2	850 mg/m^2	b.i.d. d1–14 q3w
Ducreux ASCO, 2005	CAPOX	1000 mg/m^2	b.i.d. d1–14 q3w
Cassidy *JCO*, 2004 [48]	CAPOX	1000 mg/m^2	b.i.d. d1–14 q3w
Twelves *NEJM*, 2005 [37]	X-ACT	1250 mg/m^2	b.i.d. d1–14 q3w
Scheithauer *JCO*, 2003	CAPOX	1000 mg/m^2, 1750 mg/m^2	b.i.d. d1–14 q3w, b.i.d. d1–7 q2w
Schmoll ASCO, 2005 [59]	XELOXA	1000 mg/m^2	b.i.d. d1–14 q3w
Bendell ASCO, 2006	CAPOX + bevacizumab	1000 mg/m^2 reduced to 850 mg/m^2	b.i.d. d1–5, 8–12 q2w

Table 9 Dose reductions in pivotal clinical studies of capecitabine

Indication	XELODA approved dose[a]	Median dose in pivotal trial	Percent dose reductions in pivotal trial
Metastatic colorectal cancer [6]	1250 mg/m^2 b.i.d. × 14 days q 21 days	1000 mg/m^2	40.5
Adjuvant colorectal cancer [37]	1250 mg/m^2 b.i.d. × 14 days q 21 days	1163 mg/m^2	42
Metastatic breast cancer (single agent) [74]	1250 mg/m^2 b.i.d × 14 days q 21 days	1255 mg/m^2	None reported
Metastatic breast cancer (XT) [82]	1250 mg/m^2 b.i.d. × 14 days q 21 days	963 mg/m^2	65

[a]XELODA (capecitabine) Prescribing Information. Nutley: Roche Laboratories; 2006.

were too toxic (d1–14, q3w) and 850–1000 mg/m^2 b.i.d. were more tolerable (Table 8) [37,48,59]. The reasons for this discrepancy are not known, but are believed to be related to the US diet fortified with folic acid and that folic acid exacerbates capecitabine toxicity, compliance or some genetic variations. Better understanding for this discrepancy is warranted in future studies.

It is important to appreciate that the combination of capecitabine with agents such as irinotecan and oxaliplatin is more than just replacing the backbone of 5-FU. There is a molecular rationale: XELIRI → capecitabine inhibits Bcl-2, a protein that prevents tumor cell death (apoptosis) by radiation, taxanes, oxaliplatin, and irinotecan, and XELOX → capecitabine inhibits ERCC-1, a DNA repair protein that blocks the cytotoxic activity of radiation and oxaliplatin. In addition, irinotecan and oxaliplatin induce TP in tumors. Similarly, our group has also investigated the effect of radiation on TP and showed that radiation upregulates TP in tumors, but not in normal cells. This combined modality then synergizes in both directions: radiation as chemosensitizer by upregulating TP and capecitabine after conversion to 5-FU radiosensitizing the tumor to radiation effects. This combination is of utmost interest in clinical investigation in many tumors, especially rectal cancer.

Capecitabine could replace infusional 5-FU/LV as the combination partner for oxaliplatin. XELOX offers improved convenience over regimens incorporating infusional 5-FU as this regimen entails a patient to visit the clinic only once in every 3 weeks for oxaliplatin administration. The XELIRI regimen is, however, generally not used outside a clinical trial at present because of the increased toxicity seen in the studies. A higher rate of early toxic deaths in the XELIRI led to dose reduction of irinotecan from 100 to 80 mg/m^2 days 1 and 8 without compromising efficacy.

It is also important to appreciate that dose reductions in pivotal studies both in colorectal and breast cancer indicated that dose reduction did not reduce the efficacy of capecitabine (Table 9) [6,37,74,82]. Currently, 2500 mg/m^2 is the FDA-approved dose of capecitabine but this dose is not tolerated by patients in the US. Another issue related to the dose is the two different strengths of capecitabine (150 and 500 mg). Some physicians prefer to prescribe the dose with 500 mg capsules only to prevent any overdose or underdose by a patient. We also suggest that the dose should be rounded to the closest figure to make a dose that contains a similar strength of capecitabine capsules for convenience and to decrease the risk as noted above.

Managing toxicity in capecitabine underlines the importance of educating the patient and the caretaker. Drug interactions should be borne in mind as detailed in the paper. Data on patients with DPD deficiency and tolerance of capecitabine are scarce. We suggest that it is still important to suspect and test for DPD deficiency in patients on capecitabine with any manifestation of toxicity.

In summary, most current data indicate that capecitabine is not inferior to infusional 5-FU and offers added benefit of convenience. Future studies should also aim at evaluating the drug cost. For those parts of the world in which hospitalization is required to deliver fluorouracil by infusion, an outpatient oral regimen has an advantage. Capecitabine offers not only efficacy in different gastrointestinal and non-gastrointestinal malignancies, but also broadens the availability and convenience of treatment.

Conclusion

Capecitabine is currently the only novel, orally home-administered fluorouracil prodrug. It offers patients more freedom from hospital visits and less inconvenience and complications associated with infusion devices. Furthermore, the drug compares favorably with fluorouracil in patients with advanced or metastatic colorectal cancer and pretreated breast cancer, with a safe toxicity profile, consisting mainly of gastrointestinal and dermatologic adverse effects. Whereas gastrointestinal events and HFS occur often with capecitabine, the tolerability profile is comparatively favorable. Prompt recognition of severe adverse effects is the key to successful management of capecitabine. Ongoing and future clinical trials will continue to examine, and likely expand, the role of capecitabine as a single agent and/or in combination with other anticancer agents for the treatment of other solid tumors, both in the advanced palliative and adjuvant settings.

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