Pharmacology and therapeutic efficacy of capecitabine: focus on breast and colorectal cancer

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Capecitabine (N^4-pentyloxycarbonyl-5-deoxy-5-fluorocytidine), an oral prodrug of 5-fluorouracil, has provided compelling efficacy data for the treatment of metastatic breast cancer and stage III or IV colorectal cancer, both as monotherapy and in combination regimens. The preferential conversion of capecitabine to 5-fluorouracil in neoplastic tissues renders this fluoropyrimidine particularly appealing for clinical use. The enzyme thymidine phosphorylase, which mediates the final step of the capecitabine activation pathway, is expressed in higher concentration in neoplastic than in healthy tissues. This makes capecitabine more tumor specific than other chemotherapeutic agents. Accordingly, capecitabine is generally well tolerated. In particular, the incidence of myelosuppression and alopecia is low, and the most common side effects, hand–foot syndrome and diarrhea, are usually manageable. Given its good toxicity profile, capecitabine was assessed in combination with several chemotherapeutic or biologic agents. In addition, the observation that thymidine phosphorylase is upregulated after treatment with other anticancer drugs, namely taxanes, provided a rationale for the prominent antitumor activity recently observed for the combination of capecitabine with these agents. This review provides an evidence-based update of clinical trials investigating the role of capecitabine in the treatment of breast and colorectal cancer, with special emphasis on pharmacological and safety issues that form the basis of currently used schedules. *Anti-Cancer Drugs* **20:217–229 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Pharmacological research has investigated several strategies aimed at obtaining organ-selective or tissue-selective delivery of anticancer chemotherapy. One of these is the development of prodrugs, agents with little or no pharmacological activity, undergoing biotransformation to a therapeutically active metabolite [1].

Capecitabine (N^4-pentyloxycarbonyl-5-deoxy-5-fluorocytidine; Xeloda, F. Hoffmann La-Roche, Basel, Switzerland), an orally administered fluoropyrimidine carbamate precursor of 5-fluorouracil (5-FU), has gained a top position among successful prodrugs [2–4].

Capecitabine was initially developed as an oral agent that could mimic the action of infusional 5-FU to overcome some inconveniences because of the intravenous (i.v.) administration of the therapy [5]. In addition, with the aim of obtaining greater selectivity, capecitabine was designed to be converted to 5-FU preferentially on the tumor site after a three-step enzymatic pathway [6].

Pharmacodynamic and pharmacokinetics properties

Capecitabine is a target-specific oral fluoropyrimidine that is stable in tablet form and soluble in water. After absorption of the intact molecule through the intestinal mucosa, capecitabine is hydrolyzed in the liver to 5′-deoxy-5-fluorocytidine by carboxylesterase. Subsequently, cytidine deaminase, an enzyme found in the liver and tumor tissue, converts 5′-deoxy-5-fluorocytidine to the intermediate metabolite 5′-deoxy-5-fluorouridine (5′-DFUR). In the final step, 5′-DFUR is hydrolyzed to the active drug 5-FU by thymidine phosphorylase (TP), an enzyme present in approximately three- to ten-fold higher concentration in tumor cells compared with normal cells [6,7]. This allows a selective release of 5-FU with subsequent conversion to 5-fluorodeoxyuridine monophosphate and 5-fluorouridine triphosphate. 5-FU exerts its cytotoxicity through incorporation of 5-fluorouridine triphosphate into replicating RNA as a false nucleotide and through thymidine depletion after thymidylate synthase (TS) inhibition by 5-fluorodeoxyuridine monophosphate [8]. The activity of TS is the rate-limiting step in thymidine synthesis. Without thymidine, DNA replication cannot occur and cells undergo apoptosis. Dihydropyrimidine dehydrogenase (DPD), which is highly expressed in liver, is responsible for the degradation of 5-FU, converting it to dihydro 5-FU.

The pharmacokinetics (PK) of capecitabine as a single agent was initially investigated in several phase I trials in patients with advanced and/or metastatic cancer [9,10].

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After oral administration of 1250 mg/m^2, capecitabine is rapidly absorbed from the gastrointestinal tract. The median time to reach peak concentration (t_{max}) of intact capecitabine and 5′-DFUR is 2 h, with a peak plasma drug concentration (C_{max}) of 2.5–4 mg/l. Subsequently, concentrations decline rapidly with a relatively short elimination half-life ($t_{1/2}$ less than 1 h) [10,11].

Elimination of capecitabine and its metabolites is primarily renal, whereas only a small fraction is excreted in the feces [12]. Caution is therefore necessary when capecitabine is administered in patients with renal impairment. In a study investigating the influence of creatinine clearance on the PK and safety of capecitabine, all patients with severe renal impairment experienced drug-related grade 3 or 4 adverse events (AEs) [13].

To investigate the possible influence of hepatic dysfunction on the gastrointestinal absorption of capecitabine and on its metabolism, a study was conducted on patients with mild-to-moderate disturbance of liver biochemistry because of liver metastases [14]. Although results should be read with caution because of the small sample size of the study ($n = 27$), no clinically significant influence of mild-to-moderate liver dysfunction was observed on the PK parameters of capecitabine and its metabolites.

Safety and toxicity

With the Food and Drug Administration/European Medicines Agency-approved schedule and dosing of capecitabine as single agent for colorectal cancer (CRC) or breast cancer (BC) (i.e. 1250 mg/m^2 twice daily for 14 consecutive days followed by a 1-week rest in a 3-week cycle), the drug has been demonstrated safe and generally well tolerated. However, identifying those patients who are most likely to be harmed by capecitabine is crucial. Patients with severe renal dysfunction, malabsorption syndromes, active gastrointestinal bleeding or lack of physical integrity of the upper gastrointestinal tract, and those with known DPD deficiency should not be offered the oral fluoropyrimidine.

Concomitant drug-therapy assessment is also important, as several compounds have been reported to potentially interfere with capecitabine's metabolism. For example, plasmatic phenytoin levels could increase during treatment [15] and, therefore, should be accurately monitored. In addition, capecitabine treatment may increase plasma warfarin levels and its clinical activity as an anticoagulant [16–18]. A wash-out of at least 4 weeks is recommended before starting capecitabine if the patient has received sorivudine or brivudine as antiviral therapy, a potent DPD inhibitor being their main metabolite 5-bromovinyluracil [19].

Interestingly, having received weekly 5-FU is also a risk factor for severe capecitabine toxicity [20]. The exact mechanism for this sequence-specific toxicity is unknown, but interaction with intracellular retained folate is a possibility.

In view of the growing cancer incidence and the increasing trend toward older median age in Western societies, drug tolerability in the elderly is also an important issue [21]. A number of studies have specifically focused on safety and tolerability of fluoropyrimidine alone or in combination in the older BC [22–25] or CRC populations [26,27]. According to 5-FU safety data, single-agent capecitabine [22,28–31] or capecitabine-based combinations [24,32,33] have been well tolerated too. Overall, key messages rising from available trials are reassuring. Even for older cancer patients drug toxicity is limited, and potential side effects easily manageable with appropriate patient selection [34]. In addition, data from age-unrestricted clinical trials do not support strong evidence for increased toxicity frequencies among older (> 65 years) BC or CRC patients compared with the younger populations, although it has been recognized that patients aged 80 years or above may experience a higher rate of severe toxicities.

However, even common and easily manageable side effects merit a note of caution when occurring in older patients, because of the risk of dehydration related to diarrhea and the potential reduction of capecitabine clearance according to age [34].

Upper and lower gastrointestinal toxicities, including nausea, vomiting, diarrhea, mucositis, abdominal disturbances, dyspepsia, and anorexia are frequently reported among patients exposed to capecitabine, and may simultaneously occur, according to the view of the alimentary tract mucosa as a whole entity [35]. Some comprehensive reviews have addressed and exhaustively covered this point [36,37].

Capecitabine catabolism and its deactivation depend on a specific enzymatic pathway driven and limited by DPD. The possible variability in this enzyme activity heavily influences systemic exposure to fluorodeoxyuridine and consequently the incidence of AEs related to the treatment [38]. Population studies have shown that DPD activity in nearly 0.1 and 5% of American people are completely or partially deficient, when patients with decreased enzyme expression are treated with DPD inhibitors they may present severe toxicities related to DPD deficiency [39]. However, the value of routine screening for DPD deficiency in the clinical practice remains questionable [40]. Being aware of the fact that specific DPD expression plays a critical role in determining toxicities for patients exposed to capecitabine [41] and a number of techniques have recently been developed to

categorize patients' risks at baseline and to avoid excessive toxicities [42], specific capecitabine-induced toxicities merit a special mention.

Hand–foot syndrome (HFS) is the most common dose-limiting toxicity of capecitabine, reported in up to 50% of treated patients with a median time to onset of less than 3 months. Even if not life threatening, HFS can negatively impact on patients' welfare severely disrupting their quality of life, and it is a major cause of both dose reduction and treatment discontinuation. Although HFS mechanism remains unclear, there are three chief pathogenetic hypotheses: (i) the high levels of TP and DPD in skin keratinocytes, resulting in capecitabine's metabolite accumulation [43]; (ii) the elimination of capecitabine by the eccrine system and an increased number of eccrine glands in hand and foot skin; (iii) the increased blood flow and temperature in hands and feet. In addition, the high proliferation rate of epidermal basal cells in the palm could make them more sensitive to the local action of capecitabine [43]. In fact, a recent report showed no significant association between intratumoral TP or DPD levels and frequency, severity or time to occurrence of HFS [44].

No evidence-based treatment has clearly shown superiority in controlling HFS. Clinical studies have tested the role of topical emollients and creams (that remain widely adopted medical measures), corticosteroids, nicotine patch, vitamin E supplementation, pyridoxine, and COX-2 inhibitors, whereas the role of molecules inhibiting DPD is currently under investigation [45]. Without randomized, controlled trials, the best strategy for the management of this disturbance remains treatment interruption or dose reduction. Moreover, patients should be educated in recognizing the side effect and should promptly inform their physicians.

Given the increasing median age of cancer patients and the incidence of cardiovascular diseases in elderly patients, potential cardiac toxicity induced by 5-FU has been extensively studied [46], and possibly similar cardiac effects of capecitabine must be taken into consideration. Arteriolar spasm of the coronary vessels resulting in transient ischemia is the most accredited among putative pathogenetic mechanisms for 5-FU cardiac damage [47,48].

The observed frequency of 5-FU cardiac toxicity ranges from 1.2 to 18% [49] and is largely schedule dependent [50]. After exposure to capecitabine, cardiac side effects have been reported with a frequency and pathogenesis that resemble those of 5-FU [51], but the cardiac safety profile of the oral prodrug is less defined. Chest pain has been reported in up to 6% of patients receiving single-agent capecitabine, whereas dysrhythmias or myocarditis have been reported in less than 0.1% [49].

Overall, capecitabine-related AEs in BC patients were typically mild to moderate and easily manageable with treatment interruption or dosage adjustments. The most frequently reported nonhematological toxicities were HFS (median 13%, range 0–42%), diarrhea (median 7.5%, range 0–30%), nausea (median 6.5%, range 0–35%), mucositis (median 6%, range 0–12%), and vomiting (median 4%, range 0–19%) [52]. Interestingly, in the national French compassionate-use program [53], the chance of severe HFS appeared to be dose related, being 20% in BC patients initially treated with 2500 mg, but only 2% if the initial dose was lower.

In first-line treatment, classical CMF (cyclophosphamide/methotrexate/5-FU) was compared with two different schedules of capecitabine given continuously (1300 mg/m^2 daily, days 1–21 q21) or intermittently (2000 mg/m^2 daily, days 1–14 q21) [54]. Febrile neutropenia, infection, and mucositis were more common with CMF, whereas HFS was more common with capecitabine.

Cancer and Leukemia Group B/Clinical Trials Support Unit 49907 trial revealed inferiority of capecitabine (1000 mg/m^2 twice daily on days 1–14 every 3 weeks for 6 cycles) compared with CMF (six cycles at standard doses) or doxorubicin/cyclophosphamide (AC, four cycles at standard doses) in early BC patients aged 65 years or above [25]. Toxicity was overall moderate; i.v. chemotherapy caused more myelosuppression, whereas capecitabine caused more HFS. Of note, two drug-related deaths were reported in patients treated with capecitabine.

The role of single-agent capecitabine after exposure to anthracyclines and taxanes was tested in 162 patients who received a total daily dose of 2500 mg/m^2 [55]. Grade 1 or 2 HFS, fatigue, or gastrointestinal side effects were frequently reported. Nevertheless, severe diarrhea or HFS was limited to 10% of the patients. Limited hematological toxicity and the favorable overall safety profile as single-agent have encouraged the combination of capecitabine with either taxanes, anthracyclines, or both.

A phase III trial involving 511 patients [56] showed that the combination of capecitabine and docetaxel was significantly superior to docetaxel alone. Overall, more severe AEs occurred with combination therapy (71 vs. 49%, respectively), whereas grade 4 AEs were slightly more common with docetaxel (31 vs. 25% with combination). Gastrointestinal side effects and HFS were higher in the combination arm. Interestingly, a recent retrospective analysis of this trial evaluated the impact of dose reduction on safety and efficacy of combination therapy [57]. Time to progression (TTP) and overall survival (OS) in patients who had dose reductions for AEs were similar to those of the overall study population, suggesting that reducing dose of the combination does

not compromise efficacy. These results are consistent with other phase II studies of taxanes that used doses of capecitabine lower than the usual [58–62].

Once established that single-agent capecitabine is one of the reference regimens for anthracycline/taxane pretreated BC patients, it is important to consider data on safety for newer capecitabine-based combinations.

Several phase II studies tested capecitabine and trastuzumab in HER2-overexpressing metastatic BC patients and they did not show additional unexpected toxicity from the combination over single-agent capecitabine [63–69].

Safety data from a large randomized phase III trial showed that the addition of bevacizumab to capecitabine neither affected the overall frequency nor the severity of capecitabine toxicities, nor altered its mean delivered dose intensity [70]. However, more cardiovascular events were reported for patients who received the combination (seven cases of congestive heart failure or cardiomyopathy in patients who received capecitabine and bevacizumab vs. two cases of cardiovascular events in patients receiving capecitabine only). The small number of cardiac events does not allow definitive conclusions, but a note of caution is necessary.

In the last decade, three randomized trials [30,71,72] have shown efficacy equivalence between 5-FU/leucovorin and capecitabine, with a favorable toxicity profile, strongly suggesting that the oral prodrug could replace its parental compound.

When given upfront to advanced CRC patients, single-agent capecitabine produced lower incidence of diarrhea (47.7 vs. 58%), stomatitis (24.3 vs. 61.6%), nausea (37.9 vs. 47.6%), alopecia (6 vs. 20.6%), and grade 3 or 4 neutropenia (1.2 vs. 10.3%) compared with bolus 5-FU [30]. Furthermore, cost effectiveness was in favor of capecitabine [73], with no evidence of decreased efficacy in patients requiring dose reductions.

In the adjuvant setting, a preplanned safety analysis of the X-ACT trial (see below) [74] showed that capecitabine has an improved safety profile compared with bolus i.v. 5-FU/LV, paralleling clinical toxicities observed in the metastatic setting. In the X-ACT study [72], capecitabine produced less-severe gastrointestinal toxicity, infection, neutropenia, and thrombocytopenia and was associated with significantly lower rate of grade 3/4 AEs versus 5-FU/LV. Moreover, capecitabine was equally well tolerated among older and younger patients, maintaining the safety advantage in these subgroups.

A number of randomized trials have compared oral versus i.v. fluoropyrimidines in combination with oxaliplatin as first-line [75–79] or second-line treatment [80]. These studies showed similar efficacy with a favorable toxicity profile when capecitabine was used instead of infusional 5-FU. However, the total daily dose usually prescribed in Europe (2000 mg/m^2) was less tolerated by American patients, and the economic advantage of capecitabine–oxaliplatin combination is currently uncertain [81].

Capecitabine-based combinations were proposed as alternatives to 5-FU-based regimens in the adjuvant treatment of CRC patients in three major ongoing clinical trials.

The study NO16968 (XELOXA) randomized 1864 stage III CRC patients to 5-FU/LV (either Mayo Clinic or Roswell Park schedule) or XELOX (oxaliplatin 130 mg/m^2 on day 1, capecitabine 2000 mg/m^2 daily on days 1–15 on a 3-week schedule) after surgical resection. Treatment duration for both arms was 24 weeks. In the preplanned safety analysis [82], XELOX showed fewer grade 3–4 hematological toxicities and more grade 3–4 gastrointestinal side effects compared with Mayo regimen, whereas a reverse pattern was reported when XELOX was compared with Roswell Park. As expected, grade 3 or 4 sensorial neurotoxicity and grade 3 HFS were more common in patients exposed to the XELOX regimen.

QUASAR-2 was initially designed as a three-arm randomized trial comparing single-agent capecitabine, capecitabine plus irinotecan, or capecitabine plus irinotecan, and bevacizumab. Later on, the original design was modified. The trial is currently ongoing with a target selection of 2240 CRC patients randomized to capecitabine or capecitabine and bevacizumab.

In the AVANT trial, 3450 high-risk stage II or stage III CRC patients were randomized to receive standard FOLFOX for 12 cycles or the same plus bevacizumab (5 mg/kg on day 1 every 2 weeks) followed by eight cycles of bevacizumab (7.5 mg/kg on day 1 every 21 days) or XELOX (capecitabine 1000 mg/m^2 twice daily, oxaliplatin 130 mg/m^2 every 21 days) plus bevacizumab (7.5 mg/kg on day 1 on a 3-week schedule) followed by eight cycles of bevacizumab (same dose). Safety and efficacy results of all these important trials are eagerly awaited.

Efficacy and activity

Breast cancer

In Europe and the United States, capecitabine monotherapy is indicated for the treatment of patients with locally advanced or metastatic BC after failure of taxanes and an anthracycline-containing chemotherapy regimen or when further anthracycline therapy is not indicated. In addition, capecitabine in combination with docetaxel is indicated in the treatment of patients with locally advanced or metastatic BC after the failure of anthracycline-containing chemotherapy.

Several trials investigated the role of capecitabine as single agent or in combination, as first-line therapy or in previously treated patients with advanced or metastatic BC. Key results of mainstay phase III trials are summarized in Table 1.

The role of capecitabine in the adjuvant/neoadjuvant treatment of early BC is under evaluation, exploring different schedules, sequential versus combination regimens, and specific strategies for elderly patients [87].

Single-agent capecitabine

Phase II and III trials showed that capecitabine monotherapy is active and effective in patients with metastatic BC. Although the majority of the trials was conducted in patients with anthracycline-treated and/or taxane pretreated disease, capecitabine also showed efficacy as first-line therapy.

In the pivotal phase II noncomparative study [55], 162 patients with anthracycline-refractory and paclitaxel-refractory metastatic BC received single-agent oral capecitabine (2510 mg/m^2 daily, on days 1–14 every 3 weeks). The encouraging results of this trial in terms of response rate (RR, 20%), duration of response (8.1 months), and TTP (3.1 months) formed the bases for capecitabine approval in this setting. Subsequently, several additional phase II studies were conducted confirming the initial results [22,88–93]. In addition, consistent findings were recently obtained from the analysis of an open-label expanded access program of capecitabine in patients with metastatic BC previously treated with at least two chemotherapy regimens [94].

Of note, retrospective studies have investigated whether predictive factors exist that could affect the benefit from capecitabine monotherapy in patients with metastatic BC [95–97]. Interestingly, TP tumor expression, combined TP/DPD score, hormonal receptor status, presence of visceral disease, performance status, and previously received chemotherapy seemed valuable in predicting the clinical outcome after treatment with capecitabine. All these factors deserve further investigation in larger trials.

Data on capecitabine monotherapy as first line are limited, although a recent randomized phase III trial showed a survival benefit versus oral CMF. The ANZ 0001 trial, conducted by the Australian New Zealand Breast Cancer Trials Group, compared classical CMF with two different schedules of capecitabine: intermittent capecitabine (2000 mg/m^2 daily, days 1–14 every 3 weeks), or continuous capecitabine (1300 mg/m^2 daily, days 1–21) [54]. The study enrolled 323 patients with advanced BC and compared efficacy and tolerability across the three treatment regimens. No differences were observed in terms of RR, progression-free survival (PFS), OS, and toxicity profile between intermittent and continuous capecitabine therapy. The two capecitabine arms altogether were then compared with CMF. Although no benefit in terms of RR and PFS was obtained, patients treated with capecitabine experienced better OS than patients receiving CMF [hazard ratio (HR): 0.72, 95% confidence interval (CI): 0.55–0.94, P=0.02]. In addition, capecitabine provided a better toxicity profile versus CMF, translating into improved quality of life. According to these results, capecitabine monotherapy can be considered an appropriate first-line treatment choice for patients who are not suited for intense chemotherapy or prefer oral chemotherapy [98]. Capecitabine monotherapy was also evaluated earlier in the disease course [87].

Mature results of the Cancer and Leukemia Group B 49 907 study were presented at the 2008 Annual ASCO meeting [25]. This randomized phase III trial was designed to answer the question of whether capecitabine is as effective as combination adjuvant chemotherapy in patients above 65 years of age with T1 (> 1 cm)-T4, N0-3, M0 BC. The study compared four cycles of AC or

Table 1 Phase III landmark trials in advanced/metastatic breast cancer

Reference	Treatment line	Treatment regimens	Patients	Primary endpoint	RR (%)	PFS (months)	TTP (months)	OS (months)	Previous anthracycline treatment (%)
[56]	I to III	D vs. DX	511	TTP			4.2 6.1[a]	11.5 14.5[a]	100
[54]	I	X CMF	325	QAPFS	21 18	7 7		22[a] 18	Approximately 15
[83]	I	EP vs. XP	340	PFS	41.0 41.5	11.8 12.3			Approximately 20
[84]	II	X vs. XH	156	TTP		5.6 8.5		19.9 20.3	100
[70]	I to > III	X vs. XB	462	PFS	9.1[a] 19.8	4.17 4.86		14.5 15.1	100
[85]	>I	X vs. XL	324	TTP	14[a] 22		4.4 8.4[a]		Approximately 97
[86]	I to >III	X vs. XI	752	PFS		4.2 5.8[a]			Approximately 97

B, bevacizumab; CMF, cyclophosphamide methotrexate 5-fluorouracil; D, docetaxel; E, epirubicin; H, trastuzumab; I, ixabepilone; L, lapatinib; OS, overall survival; P, paclitaxel; PFS, median progression-free survival; QAPFS, quality-adjusted progression-free survival; X, capecitabine; RR, response rate; TTP, median time to progression.
[a]Statistically significant.

six cycles of CMF to capecitabine (1000 mg/m^2 twice daily on days 1–14 every 3 weeks for six cycles), and the choice of AC or CMF as standard therapy was on a case-by-case basis at the investigator's discretion.

On the basis of the activity of capecitabine in women with advanced BC, an innovative non-inferiority design was adopted with the hope that oral chemotherapy could be as effective as standard i.v. therapy in adjuvant treatment of older patients. According to an adaptive sample size calculation based on Bayesian prediction, 633 patients were randomly assigned to capecitabine or AC/CMF. The primary endpoint was relapse-free survival. With a median follow-up of 2.4 years, patients receiving capecitabine had a significantly higher risk of relapse (HR: 2.09, 95% CI: 1.4–3.2, P=0.0006) or death (HR: 1.85, 95% CI: 1.1–3.1, P=0.02) than those on standard therapy.

Given the activity of capecitabine in women with chemoresistant advanced BC, the inferiority of the fluoropyrimidine in comparison with standard therapy was quite surprising, and results from other ongoing trials are eagerly awaited [87,99].

Capecitabine in combination therapy

The peculiar characteristics of capecitabine make it a good partner in combination therapies with other chemotherapeutic and biologic agents. In particular, its favorable toxicity profile, characterized by low incidence of myelosuppression and alopecia, and the synergy with other anticancer therapies, provides the rationale of combining capecitabine with other anticancer drugs [3,100].

Preclinical studies showed that taxanes could increase the levels of TP in tumor tissue [101]. This observation, recently confirmed by translational studies [102,103], led to the design of several clinical trials in which capecitabine was combined with docetaxel or paclitaxel, using different doses and schedules.

In a large international, randomized, phase III trial, patients with relapsed BC previously treated with anthracyclines were randomized to 3-weekly cycles of either: oral capecitabine 1250 mg/m^2 twice daily, on days 1–4 followed by a 7-day rest period, plus docetaxel 75 mg/m^2 on day 1 (combination arm); or docetaxel 100 mg/m^2 on day 1 (single-agent docetaxel arm) [56]. The primary goal of the study was met, with capecitabine/docetaxel showing significantly superior TTP (HR: 0.65, P=0.00019), OS (HR: 0.77, P=0.01), and RR (42 vs. 30%, P=0.006) compared with single-agent docetaxel. This multicenter, phase III study was the first clinical trial in which a cytotoxic combination regimen provided a significant survival advantage over monotherapy in patients with metastatic BC failing anthracycline therapy. Unfortunately, the trial does not allow answering the question of whether combination therapy is superior to sequential use of docetaxel and capecitabine. In fact, built-in crossover was not mandated and only 27% of patients allocated to docetaxel monotherapy received capecitabine upon progression.

Of note, improvements in OS favoring combination arm were maintained at the most updated survival analysis (HR: 0.77, P < 0.01, median 14.5 vs. 11.5 months) [104], whereas a detailed analysis showed that outcome benefits from docetaxel/capecitabine were achieved despite 65% of patients in the combination arm required dose reduction during the study period [57]. The latter study suggests that management of side effects from docetaxel/capecitabine is possible without compromising efficacy. These results are consistent with those of other phase II studies combining taxanes with reduced-dose capecitabine [58–62]. Moreover, one of these trials, through a correlative analysis of TP, corroborated the hypothesis that the tumor expression of this enzyme may represent a useful predictor of benefit from taxane-modulated capecitabine regimens [62].

A randomized phase III trial compared docetaxel plus gemcitabine to docetaxel plus capecitabine and showed similar efficacy between treatment arms, but significantly higher nonhematologic toxicity (HFS, diarrhea, mucositis) with the capecitabine-containing regimen [105]. However, as a superior design was used in the study, the sample size had to be considered inadequate to demonstrate equivalence. In addition, the greater toxicity of capecitabine/docetaxel arm may have been related to use of a higher dose of capecitabine (1250 mg/m^2 twice daily on days 1–14) than usual.

A phase III randomized study compared the efficacy of capecitabine/paclitaxel versus epirubicin/paclitaxel in patients with previously untreated metastatic BC [83]. The trial enrolled 340 patients who were randomized to receive six cycles of epirubicin (60 mg/m^2, day 1 every 3 weeks) plus paclitaxel (175 mg/m^2, day 1 every 3 weeks), or six cycles of capecitabine (2000 mg/m^2 daily on days 1–14 every 3 weeks) plus paclitaxel (175 mg/m^2, day 1 every 3 weeks). The preliminary results suggested a comparable efficacy between the two treatment arms.

Several other phase II studies tested combinations of capecitabine with other chemotherapeutic agents, such as paclitaxel [58,60,106], vinorelbine [107–110], and gemcitabine [111,112].

Capecitabine has also been investigated in combined regimens testing novel chemotherapeutic agents and molecular targeted therapies [3].

A large, phase III study enrolled 752 patients to compare the combination of the microtubule inhibitor ixabepilone

(BMS247550) plus capecitabine with capecitabine alone in the treatment of metastatic BC patients pretreated with taxane and anthracycline chemotherapy [86,113].

Patients were randomly assigned to ixabepilone 40 mg/m^2 i.v. on day 1 of a 21-day cycle plus capecitabine 2000 mg/m^2 on days 1 through 14 of a 21-day cycle, or capecitabine alone 2500 mg/m^2 on the same schedule. The primary endpoint PFS resulted significantly longer with the combination, translating into a 25% reduction in the estimated risk of disease progression ($P = 0.0003$). Of note, sensitivity analysis carried out by the FDA confirmed these findings, indicating that the advantage of the combination is robust across the entire population studied and not driven by a particular treatment group.

In the HER-2-positive disease, both trastuzumab and lapatinib were investigated in combination with capecitabine. Several phase II studies were conducted to investigate activity and feasibility of capecitabine and trastuzumab in combination in HER2-overexpressing advanced/metastatic BC [63–69]. The results varied across trials, but all studies suggested that the combination is highly active and well tolerated.

The German Breast Group 26/Breast International Group 3-05 phase III study randomized patients with HER-2-positive advanced BC, whose disease had progressed on trastuzumab, to continue or to stop trastuzumab while starting capecitabine [84]. Unfortunately, the trial was closed early when lapatinib was approved in this indication; at this point, 156 women had been randomized. Despite the early closure, the study generated strikingly clear results. Continuing rather than stopping trastuzumab with capecitabine led to improvement in TTP (8.2 vs. 5.6 months, $P = 0.03$), response rate (48 vs. 27%; $P = 0.01$), and a trend towards better survival (25.5 vs. 20.5 months; $P =$ NS).

Other strategies for targeting HER-2 after progression on trastuzumab/chemotherapy have been tested, and an interesting option is the use of the oral HER-1/HER-2 tyrosine kinase inhibitor lapatinib in combination with capecitabine.

A phase III randomized open-label trial compared lapatinib plus capecitabine versus capecitabine monotherapy in 399 patients with HER2-positive advanced BC previously treated with anthracycline-containing, taxane-containing, and trastuzumab-containing regimens [85]. The combination regimen consisted of lapatinib 1250 mg daily and capecitabine on days 1–14 of a 21-day cycle, at a total dose of 2000 mg/m^2 daily. Patients allocated to the control arm received single-agent capecitabine, administered on days 1–14 of a 21-day cycle in a divided 2500 mg/m^2 dose. The primary endpoint was TTP as assessed by independent reviewers. Updated efficacy analysis of this trial was recently reported [114], confirming that the addition of lapatinib to capecitabine significantly improves TTP (HR: 0.57, $P < 0.001$) without increasing toxicity.

Capecitabine was also evaluated in association with bevacizumab, the monoclonal antibody directed to vascular endothelial growth factor. A phase III trial compared bevacizumab (15 mg/kg every 3 weeks) plus capecitabine (2500 mg/m^2 daily on days 1–14 every 3 weeks) with capecitabine (at the same dose) in patients with heavily pretreated mainly HER-2-negative metastatic BC [70]. Although a significantly increased RR was obtained with the combination (19.8 vs. 9.1%, P=0.001), this did not translate into improved PFS or OS. The lack of benefit was hypothesized to be, at least in part, attributable to the nature of disease progression; as tumors progress, more angiogenic factors are expressed, thus tumors may escape bevacizumab treatment by using alternative proangiogenic pathways. Although clinical evidence is not yet available, this theory suggests that bevacizumab may be more effective when used earlier in the course of disease.

In the meantime, an interesting phase II trial testing the combination of metronomic oral capecitabine (500 mg thrice daily) and cyclophosphamide (50 mg daily) plus bevacizumab (10 mg/kg every 2 weeks) has been recently published [115]. In 46 evaluable patients with advanced BC, an overall RR of 48% was observed and a clinically relevant fraction of patients (68%) achieved a control of the disease for at least 6 months. The minimal toxicity together with the possibility of continuing the treatment for up to several months in responders, make this regimen particularly appealing as an additional option in the treatment of metastatic BC.

Colorectal cancer

Capecitabine has provided compelling efficacy data in the treatment of CRC, both as single-agent and in combination regimens.

Single-agent capecitabine

Two large phase III trials [29,71], enrolling about 600 patients each, showed similar efficacy between capecitabine and 5-FU in patients with metastatic CRC. Both trials had a non-inferiority design, with RR as primary endpoint. Capecitabine was administered with the schedule of 1250 mg/m^2 twice daily, days 1–14 every 3 weeks, whereas 5-FU was administered accordingly with the Mayo Clinic regimen. Rapid i.v. injection of 20 mg/m^2 LV followed by an i.v. bolus injection of 425 mg/m^2 daily, on five consecutive days every 4 weeks. In the first trial [71], RR was slightly higher for patients receiving

capecitabine compared with those receiving 5-FU (18.9 vs. 15%). Efficacy results, however, were similar between treatment arms with median time to treatment failure of 4.2 versus 4 months (P=0.89), median PFS of 5.3 versus 4.7 months (P=0.65), and median OS of 13.2 versus 12.1 months (P=0.3), respectively. Consistently, similar outcome results were reported in the second trial [29], although with a noteworthy superior RR (24.8 vs. 15.5%) for patients on capecitabine. Moreover, the oral fluoropyrimidine showed an overall better safety profile. Single-agent capecitabine, however, is usually prescribed to older patients or those with non resectable advanced disease and medical comorbidities. A pilot study [116] suggests that intratumoral gene expression levels of DPD may be useful in predicting clinical outcomes of patients treated with single-agent capecitabine.

X-ACT trial [72] aimed at comparing capecitabine to 5-FU in about 2000 stage III CRC patients after radical surgery. The trial met its primary endpoint, and showed at least non-inferiority of capecitabine in terms of DFS for the oral drug. Updated efficacy data presented at 2008 ASCO meeting [117] with a median follow-up of 7 years, confirmed that capecitabine is at least equivalent to 5-FU with a trend for superiority (P=0.06), with 5-year DFS of 60.8% for capecitabine versus 56.7% for 5-FU. Furthermore, 3 and 5-year OS and RFS were similar between the treatment arms.

Capecitabine in combination therapy

Several randomized phase III clinical trials reported similar efficacy results for capecitabine and i.v. 5-FU when combined with oxaliplatin [76–80,118], with median first-line PFS of about 9 months and median

Table 2 Phase III trials comparing capecitabine plus oxaliplatin to 5-FU plus oxaliplatin regimens for advanced CRC

Reference	Treatment line	Patients	Treatment regimens	Primary endpoint	RR (%)	Median TTP or median PFS (months)	Median OS (months)
[75]	I	348	Capecitabine 1000 mg/m^2 for 14 days, oxaliplatin 130 mg/m^2 on day 1 every 3 weeks (XELOX)	TTP	37	8.9	18.1
			vs.				
			FU 2250 mg/m^2 c.i. during 48 h on days 1, 8, 15, 22, 29, and 36 plus oxaliplatin 85 mg/m^2 on days 1, 15, and 29 every 6 weeks (FUOX)		46	9.5	20.8
[76]	I	474	Capecitabine 1000 mg/m^2 bid, days 1 to 14 plus oxaliplatin 70 mg/m^2 days 1 and 8, repeated every 22 days (CAPOX)	PFS	48	7.1	16.8
			vs.				
			Oxaliplatin 50 mg/m^2 followed by leucovorin 500 mg/m^2 plus FU 2000 mg/m^2 as a 22-h infusion days 1, 8, 15, and 22, repeated every 36 days (FUFOX)		54	8	18.8
[77]	I	306	XELOX	RR	42	9.3	19.9
			vs.				
			Oxaliplatin 100 mg/m^2 on day 1, LV 400 mg/m^2 2 h infusion 5-FU 400 mg/m^2 i.v. bolus then 2400–3000 mg/m^2 46 h infusion every 2 weeks (FOLFOX)		46	9.7	18.4
[78]	I	2034 (with or without bevacizumab)	XELOX	PFS	47	8	19.8
			vs.				
			FOLFOX-4		48	8.5	19.6
[79]	I	373 (with or without bevacizumab)	Standard FOLFOX	Incidence of grade 3–4 toxicities	41/52	8.7/9.9	19.2/26.1
			vs.				
			Oxaliplatin 85 mg/m^2 days 1 and 15, leucovorin 20 mg/m^2 and bolus 5-FU 500 mg/m^2 days 1, 8, 15 q28		20/39	6.9/8.3	17.9/20.4
			vs.				
			XELOX		27/46	5.9/10.3	17.2/24.6
[118]	I	322	Capecitabine 1000 mg/m^2 on days 1–11 plus oxaliplatin 100 mg/m^2 on day 1 every 14 days (OXXEL)	RR, PFS	34	6.6	16
			vs.				
			Oxaliplatin 85 mg/m^2 on day 1, leucovorin 250 mg/m^2 followed by plus FU 850 mg/m^2 bolus on day 2, repeated every 14 days (OXAFAFU)		33	6.5	17
[80]	II	627	XELOX	PFS	20	4.8	11.9
			vs.				
			FOLFOX-4		18	4.7	12.6

5-FU, 5-fluorouracil; CRC, colorectal cancer; c.i., continuous infusion. i.v., intravenous; OS, overall survival; PFS, median progression-free survival; RR, response rate; TTP, median time to progression.

OS of about 19 months. Detailed information on the role of capecitabine combined with oxaliplatin was reviewed elsewhere [119]. Nevertheless, key outcome results of those trials are summarized in Table 2, together with efficacy results of the TREE-2 study (see below). There is a growing interest for the use of fluoropyrimidine-based regimens in combination with bevacizumab.

The TREE study was initially designed to investigate the role of oxaliplatin in first-line treatment for CRC patients with three different fluoropyrimidine regimens: standard FOLFOX, bFOL (oxaliplatin 85 mg/m^2 days 1 and 15, leucovorin 20 mg/m^2 and bolus 5-FU 500 mg/m^2 days 1, 8, 15 q28) or CapeOx (oxaliplatin 130 mg/m^2 day 1, capecitabine 1000–850 mg/m^2 for 14 consecutive days on a 3-week schedule). After 150 patients had been enrolled, data regarding bevacizumab efficacy became available. At that point the trial was amended, and 213 more patients were randomized to the same arms plus bevacizumab 2.5 mg/kg/week accordingly to the treatment schedules. The primary endpoint of the study was the incidence of grade 3–4 toxicities during the first 12 weeks of therapy. In TREE-1 (the first cohort), the incidence of any grade 3–4 toxicity in FOLFOX arm was 75%, bFOL 42%, and CapeOx 73%, whereas in TREE-2 the same figures were 66, 59, and 54%, respectively. Importantly, the addition of bevacizumab to each arm was associated with more hypertension, impaired wound healing and bowel perforation, but with an overall acceptable toxicity profile.

Patients with high-risk stage II or stage III CRC who had undergone curative surgery are at high risk for recurrence. Several clinical trials (such as XELOXA, AVANT, SCOT, QUASAR-2) are currently ongoing, with the aim to investigate the potential role of capecitabine combined with either oxaliplatin or bevacizumab or both in the adjuvant setting. The primary endpoint of all those studies is DFS, whereas safety and OS are co-secondary endpoints. Efficacy results, however, are not yet available.

The efficacy of capecitabine in association with oxaliplatin, bevacizumab, and cetuximab was investigated in the CAIRO-2 [120], a large phase III study conducted by the Dutch Colorectal Cancer Group. CAIRO-2 randomized over 700 untreated CRC patients to receive the XELOX regimen (capecitabine 1000 mg/m^2/twice daily on days 1–14 q21 + oxaliplatin 130 mg/m^2 on day 1 q21) plus either bevacizumab alone (7.5 mg/kg on day 1 q21) or bevacizumab at the same dose with cetuximab (cetuximab 400 mg/m^2 on day 1, followed by 250 mg/m^2 given weekly). Although median OS did not differ (20.4 vs. 20.3 months), PFS was significantly shorter for patients who received both antibodies (9.6 vs. 10.7 months, P=0.018), with a 20% increase in the risk of disease progression. Moreover, the double monoclonal antibody regimen carried the greatest risk of grade 3 and 4 toxicity, especially diarrhea.

The combination of capecitabine and irinotecan has been shown to be highly active in preclinical models, with minimal overlapping toxicities and non-cross-resistance. A number of phase II trials have emerged, testing the combination in the advanced setting [121–124] and demonstrating its activity. A note of caution, however, should be considered regarding the correlation between drug dosage and the risk of severe diarrhea.

Of note, in a capecitabine/irinotecan combination trial, Meropol *et al.* [125] evaluated TP, TS, and DPD as predictors of therapeutic benefit in first-line metastatic setting. Interestingly, positive immunostaining for TP was associated with a higher RR (65 vs. 27%) to the CAPIRI combination, and TTP was significantly longer (8.7 vs. 6.0 months) in the patients with TP-positive disease. Conversely, neither TS nor DPD, both enzymes that have been previously shown to correlate with resistance to 5-FU, were able to predict response to capecitabine plus irinotecan. These data reinforce the hypothesis that TP may have a unique role as a predictive factor according to its key role in the activation pathway of capecitabine. Randomized comparisons testing capecitabine–irinotecan combinations are much less evidence based, if not disappointing. A multicenter randomized phase III trial compared FOLFIRI, mIFL, or CAPIRI in metastatic CRC as first-line treatment. FOLFIRI and mIFL showed a more acceptable toxicity than CAPIRI with fewer occurrences of severe diarrhea, dehydration, nausea, and vomiting. The arm with capecitabine was closed when bevacizumab was added to the regimens on study [126]. In terms of efficacy, FOLFIRI showed better results in PFS and OS compared with the other arms.

EORTC 40015 planned to randomized nearly 700 CRC patients, previously untreated for advanced disease, to irinotecan 250 mg/m^2 day 1 plus capecitabine 1000 mg/m^2 on days 1–14 every 21 days or to standard treatment with fortnightly 48-h infusional 5-FU and leucovorin plus irinotecan 180 mg/m^2, day 1, every 2 weeks (FOLFIRI), and than to placebo or celecoxib.

Unfortunately, the large phase III trial was prematurely closed because of an unexpected high rate of tumor-unrelated deaths in the first 85 enrolled patients [127]. On account of the small sample size after early termination, no definitive conclusion can be drawn in relation to the non-inferiority of CAPIRI compared with FOLFIRI.

As reported at 2007 Gastrointestinal Cancers Symposium by the AIO CRC Study Group, both capecitabine with irinotecan and capecitabine with oxaliplatin seemed

to be active and well tolerated when combined with cetuximab [128].

Conclusion

Several trials demonstrated clinical benefit from capecitabine monotherapy or in combination with other agents for the treatment of BC and CRC.

Capecitabine presents a favorable safety profile. The incidence of myelosuppression and alopecia is particularly low, and the most common side effects, HFS and diarrhea, are usually manageable. The oral formulation is an additional benefit, as demonstrated by studies investigating patients' preference for orally administered chemotherapy over i.v. regimens [129–131].

Of note, capecitabine was designed as an orally administered prodrug to be converted into the cytotoxic agent 5-FU. The last step of this metabolic pathway is the enzyme TP, expressed in a higher concentration in neoplastic than healthy tissues. This makes capecitabine more tumor specific than other chemotherapeutic agents.

In addition, there is evidence that TP can be upregulated by other chemotherapeutic agents. This observation is in line with the successful results obtained by some chemotherapy regimens in which the combined or sequential use of TP-targeting (e.g. capecitabine) and TP-modulating (e.g. taxanes) agents translate into a synergistic effect. This 'bench to bedside' link and the demonstration of the proof of principle are obviously of paramount relevance.

Therefore, clinical and translational studies specifically designed on the basis of this rationale should be warmly encouraged. In the era of targeted therapy, it is tempting to hypothesize that targeted chemotherapy may also exist, and great effort should be dedicated to improve our knowledge of potential targets.

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