Original article

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First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin

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On behalf of the Capecitabine Colorectal Cancer Study Group

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Purpose: To evaluate the safety profile of capecitabine using data from a large, well-characterized population of patients with metastatic colorectal cancer treated in two phase III studies. In these trials, capecitabine achieved significantly superior response rates, equivalent time to disease progression and equivalent survival compared with 5-fluorouracil (5-FU)/leucovorin.

Patients and methods: Patients (n = 1207) were randomized to either oral capecitabine (1250 mg/m^2 twice daily, on days 1–14 every 21 days) or intravenous (i.v.) bolus 5-FU/leucovorin (Mayo Clinic regimen).

Results: Capecitabine demonstrated a safety profile superior to that of 5-FU/leucovorin, with a significantly lower incidence of diarrhea, stomatitis, nausea, alopecia and grade 3 or 4 neutropenia leading to significantly fewer neutropenic fever/sepsis cases and fewer hospitalizations. All patients in the capecitabine group received a starting dose of 1250 mg/m^2 twice daily and the majority (66%) did not require dose modification for adverse events. In the 5-FU/leucovorin group, 58% of patients did not require dose reduction for toxicities. The capecitabine dose-modification scheme reduced the recurrence of key toxicities without compromising efficacy. In both treatment arms, patients with moderate renal impairment at baseline (estimated creatinine clearance 30–50 ml/min) experienced a higher incidence of grade 3 or 4 toxicities. This increase was more pronounced with 5-FU/leucovorin.

Conclusions: Capecitabine is at least as effective, better tolerated and more convenient than i.v. 5-FU/leucovorin as treatment for patients with metastatic colorectal cancer. Analysis of data from two large phase III trials demonstrates that efficacy is not compromised in patients requiring a dose reduction for adverse events. The phase III data and an additional pharmacokinetic study support a lower starting dose in patients with moderate renal impairment at baseline (calculated creatinine clearance 30–50 ml/min) and a contra-indication in patients with severely impaired creatinine clearance at baseline (<30 ml/min). For patients with normal or mildly impaired renal function at baseline, the standard starting dose is well tolerated. The incidence and severity of adverse events in patients with moderate renal impairment at baseline who were treated with 5-FU/leucovorin was more pronounced, indicating that capecitabine provides a better-tolerated alternative.

Key words: capecitabine, colorectal cancer, fluoropyrimidine, tolerability

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Introduction

The fluoropyrimidines, particularly 5-fluorouracil (5-FU), are widely used in the treatment of solid tumors, including breast and colorectal cancers. In response to the need for new therapeutic options offering improved efficacy, tolerability and convenience for patients, a new class of oral fluoropyrimidines has been developed. Among these, capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland), has demonstrated high activity and a favorable safety profile. Capecitabine was rationally designed to mimic continuous infusion 5-FU. It has a unique mechanism of activation that exploits the high activity of thymidine phosphorylase in malignant tissue, resulting in the generation of 5-FU preferentially in tumor tissue [1]. After oral administration, capecitabine is absorbed as an intact molecule through the intestinal tract, thus avoiding the intra-luminal release of 5-FU. This may avoid some of the gastrointestinal toxicities observed with agents that release 5-FU directly into the gastrointestinal tract, such as doxifluridine (the precursor of capecitabine), or the combination of uracil and tegafur, and leucovorin, which is known to result in a high incidence of grade 3 or 4 diarrhea [2]. Capecitabine subsequently undergoes a three-step enzymatic conversion, the final stage of which is mediated by thymidine phosphorylase. This enzyme shows significantly increased activity in tumor tissue compared with healthy tissue. It is the localization of this key enzyme that presumably leads to the tumor selectivity of capecitabine, minimizing exposure to systemic 5-FU [1, 3]. As an oral agent, capecitabine simplifies chemotherapy and provides convenient outpatient therapy that avoids the complications and discomfort associated with intravenous (i.v.) administration.

Capecitabine has been investigated extensively in clinical trials. Capecitabine monotherapy is an established treatment option for patients with anthracycline- and taxane-pretreated metastatic breast cancer [4, 5] and is active in patients with metastatic colorectal cancer [6–8]. Two large, phase III trials have demonstrated that as first-line therapy for metastatic colorectal cancer, capecitabine achieves significantly superior response rates, equivalent time to disease progression and equivalent survival compared with 5-FU/leucovorin [7, 8]. A prospectively planned, integrated analysis of the efficacy and safety data from these trials was conducted to obtain information on a large patient population (>1200). The results of the integrated analysis confirmed the results of the individual trials [9].

All phase II/III capecitabine trials have included a scheme for dose modification, including both treatment interruption and dose reduction, in the event of toxicities classified as grade 2 or higher [according to National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC)] [4]. The goal of treatment interruption and dose modification is to prevent development of more severe toxicities and to avoid the recurrence of toxicities, while maintaining efficacy at an individually adjusted dose level.

The integrated analysis of the two phase III trials in metastatic colorectal cancer has provided an opportunity to retrospectively assess the impact of the capecitabine dose-modification scheme in a large, well-characterized population of patients with metastatic colorectal cancer. This paper reviews in detail the safety profile of capecitabine, and compares the incidence and timing of dose modification and its impact on safety and efficacy in patients treated with capecitabine or 5-FU/leucovorin. The impact of moderate or severe renal impairment at baseline, defined using the Cockcroft and Gault formula [10], is also compared in the two treatment groups. In addition, the impact of age on the safety profile of capecitabine is assessed and capecitabine dosing recommendations are provided.

Patients and methods

Patients and treatment

All patients included in either trial had metastatic colorectal cancer and had not received prior cytotoxic chemotherapy for metastatic disease. Adjuvant or neo-adjuvant therapy completed at least 6 months before enrollment was allowed. Patients were randomized (1:1) to either oral capecitabine (1250 mg/m^2 twice daily for 14 days, followed by a 7-day rest period) or 5-FU/leucovorin administered according to the Mayo Clinic regimen (leucovorin 20 mg/m^2 followed by 5-FU 425 mg/m^2, administered as an i.v. bolus on days 1–5 every 28 days) [7–9].

Assessment of safety

The population for safety assessment included all patients who received at least one dose of study medication. Toxicities were assessed and recorded at every visit and graded (grade 1–4) according to NCIC CTC (version 1.0). Hand–foot syndrome was graded 1–3 [4]. Grade 1 was defined as numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema not disrupting normal activities; grade 2 was defined as painful erythema with swelling or disruption of daily activities; and grade 3 was defined as moist desquamation, ulceration, blistering, severe pain or any symptoms leading to inability to perform daily activities.

Assessment of the impact of the dose-modification scheme

The capecitabine dose-modification scheme was applied if patients experienced grade 2–4 toxicities (Table 1). In the 5-FU/leucovorin treatment group, the dose of leucovorin was not modified and the dose of 5-FU was escalated or reduced depending upon the occurrence and severity of toxicities in the preceding treatment cycle (Table 2). Dose modification was not required for toxicities that were considered unlikely to become serious or life-threatening (e.g. alopecia or altered taste) or for anemia, as this could be effectively managed with red blood cell transfusions.

The overall incidence of dose modifications, the time to first dose modification and the duration of treatment in the two treatment groups were compared, as well as the impact of dose modification on the safety profile. A retrospective, time-dependent Cox regression analysis was used to compare the risk of disease progression or death in patients with or without dose modification. This provided an indication of the impact of dose modification on efficacy.

Table 1. Capecitabine dose-modification scheme

NCIC CTC toxicity grade	Appearance	Adjustment during therapy	Adjustment for next cycle (relative to initial dose)
2	1st	Interrupt until resolved to grade 0 or 1	100%
	2nd	Interrupt until resolved to grade 0 or 1	75%
	3rd	Interrupt until resolved to grade 0 or 1	50%
	4th	Discontinue drug permanently	–
3	1st	Interrupt until resolved to grade 0 or 1	75%
	2nd	Interrupt until resolved to grade 0 or 1	50%
	3rd	Discontinue drug permanently	–
4	1st	Discontinue drug permanently or interrupt until resolved to grade 0 or 1[a]	50%

[a]At the discretion of the clinician.

NCIC CTC, National Cancer Institute of Canada Common Toxicity Criteria.

Table 2. 5-Fluorouracil (5-FU) dose modification as a percentage of preceding 5-FU dose

Hematological toxicity (grade)	Non-hematological toxicity (grade)				
	0	1	2	3	4
0	110	100	80	70	70
1	100	100	80	70	70
2	100	100	80	70	70
3	80	80	70	70	70
4	70	70	70	70	Discontinue drug permanently

Pharmacokinetic study

A population pharmacokinetic study was performed in patients receiving capecitabine. Blood samples were taken during study weeks 4 and 10, within 0.5–1.5 h, 1.5–3.0 h and 3–5 h after drug administration. Patients who vomited within 2 h of ingesting capecitabine were excluded from the pharmacokinetic analysis. Patients were also excluded if blood samples were unavailable or if the time of drug administration or blood sampling was unclear or improperly documented. The pharmacokinetics of capecitabine and its key metabolites 5′-deoxy-5-fluorouridine (5′-DFUR), 5-FU and α-fluoro-β-alanine (FBAL) were compared in retrospectively defined patient subgroups.

Impact of renal impairment and age on safety

The effect of renal function and age at baseline on the safety profile of capecitabine was also evaluated in the safety population. The incidences of grade 3 or 4 adverse events were retrospectively analyzed in patient subpopulations grouped by age and baseline creatinine clearance. Creatinine clearance was calculated according to the formula of Cockroft and Gault [10], based on sex, age, unadjusted body weight and serum creatinine concentration: for females, creatinine clearance (ml/min) = [(140-age) × weight (kg) × 0.85]/[72 × serum creatinine (mg/dl)] or [(140-age) × weight (kg) × 0.85]/[0.81 × serum creatinine (μmol/l)]. For males, creatinine clearance (ml/min) = [(140-age) × weight (kg)]/[72 × serum creatinine (mg/dl)] or [(140-age) × weight (kg)]/[0.81 × serum creatinine (μmol/l)].

Renal function was classified as normal (>80 ml/min), mildly impaired (51–80 ml/min), moderately impaired (30–50 ml/min) or severely impaired (<30 ml/min).

Results

Patient population

In total, 1207 patients were randomized to treatment with capecitabine (603 patients) or 5-FU/leucovorin (604 patients). Seven patients in the capecitabine group and 11 in the 5-FU/leucovorin group did not receive study medication and therefore the safety population included 596 patients in the capecitabine group and 593 in the 5-FU/leucovorin group.

The demographic and baseline characteristics of patients in the two groups were well balanced in terms of median age [64 years (range 23–86) in the capecitabine group and 63 years (range 24–87) in the 5-FU/leucovorin group], Karnofsky Performance status (median of 90% in both groups), and proportion of patients who had received prior adjuvant treatment (23% and 25% for capecitabine and 5-FU/leucovorin, respectively). The predominant metastatic sites were liver (72% and 73% of patients, respectively) and lung (12% and 14% of patients, respectively).

Table 3. Summary of frequently reported (≥5%) treatment-related adverse events (all grades)

	Percentage of patients	
	Capecitabine (n = 596)	5-Fluorouracil/leucovorin (n = 593)
Stomatitis[a]	24.3	61.6
Diarrhea[a]	47.7	58.2
Hand–foot syndrome[a]	53.5	6.2
Nausea[a]	37.9	47.6
Vomiting	23.3	27.0
Fatigue	21.1	25.0
Alopecia[a]	6.0	20.6
Anorexia	10.6	13.5
Abdominal pain	11.4	11.6
Pyrexia	8.4	11.6
Dermatitis	9.6	10.8
Appetite decreased	7.0	8.3
Constipation	6.7	7.9
Weakness	6.7	7.6
Neutropenia[a,b]	1.2	10.3
Dry skin	7.4	5.1
Dyspepsia	5.4	5.9
Dehydration	4.2	6.1
Lacrimation increased	6.0	4.0
Abdominal pain (upper)	6.0	3.9
Weight decrease	3.4	5.7

[a]P <0.001.
[b]Includes only laboratory abnormalities that required medical intervention.

Safety profile

Table 3 shows the distribution of treatment-related adverse events occurring in >5% of patients in either of the two treatment arms. Diarrhea, stomatitis, neutropenia leading to medical intervention, nausea and alopecia occurred significantly more frequently in the 5-FU/leucovorin arm (P <0.001), while hand–foot syndrome occurred more frequently in the capecitabine arm (P <0.001). The majority of treatment-related adverse events in both treatment arms were graded as mild to moderate in intensity. Grade 3 adverse events were more common in the capecitabine group than the 5-FU/leucovorin group (38.1% compared with 34.1%, respectively; P = 0.16), due primarily to grade 3 hand–foot syndrome. However, grade 4 adverse events were more common with 5-FU/leucovorin (3.0% and 5.1%, respectively; P = 0.078), due primarily to neutropenia-related complications and diarrhea. The most frequent grade 3 or 4 treatment-related adverse events in patients receiving 5-FU/leucovorin were diarrhea (grade 3, 10.3%; grade 4, 1.9%) and stomatitis (grade 3, 14.2%; grade 4, 0.5%). In patients receiving capecitabine, hand–foot syndrome (grade 3, 17.1%; grade 4, not applicable) and diarrhea (grade 3, 11.6%; grade 4, 1.5%) were the most commonly occurring grade 3 or 4 treatment-related adverse events (Figure 1). The incidence of grade 3 or 4 treatment-related adverse events during the first treatment cycle was significantly higher in patients receiving 5-FU/leucovorin than in those receiving capecitabine (22.6% compared with 9.1%, respectively; P <0.001).

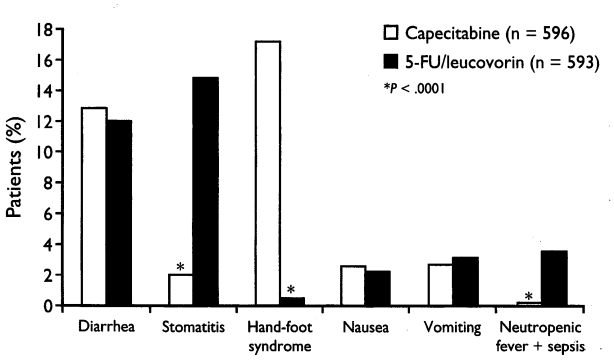

Figure 1. Most common grade 3 or 4 treatment-related adverse events in patients receiving capecitabine or 5-fluorouracil (5-FU)/leucovorin.

Table 4. Summary of all grade 3 and grade 4 liver and blood count abnormalities

Laboratory parameter	Percentage of patients			
	Capecitabine (n = 596)		5-Fluorouracil/ leucovorin (n = 593)	
	Grade 3 or 4	Grade 4	Grade 3 or 4	Grade 4
ALT elevation	0.5	0.0	0.7	0.0
AST elevation	0.7	0.0	1.2	0.0
Alkaline phosphatase elevation	3.4	0.2	4.1	0.0
Total bilirubin elevation	22.8	4.5	5.9	2.5
Anemia	2.0	0.2	1.7	0.3
Neutropenia	2.3	1.7	22.8	13.5
Thrombocytopenia	1.0	0.5	0.3	0.2
Leukopenia	37.2	7.9	40.3	9.4

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The incidence of grade 3 and 4 laboratory abnormalities (liver enzyme and blood count) is shown in Table 4. Grade 3 or 4 neutropenia was significantly more common with 5-FU/ leucovorin than with capecitabine (22.8% compared with 2.3%; P <0.001), resulting in a significantly higher incidence of neutropenic fever and sepsis (3.4% compared with 0.2%; P <0.001) with more associated hospitalizations. Grade 3 hyperbilirubinemia (1.5–3.0 × upper limit of normal) occurred more frequently in the capecitabine group (18.3% compared with 3.3%; P <0.001), but grade 4 hyperbilirubinemia (>3.0 × upper limit of normal) occurred with a similar incidence in both treatment groups (4.5% compared with 2.5%, respectively; P = 0.072). Hyperbilirubinemia tended to be an isolated laboratory abnormality involving almost exclusively the indirect bilirubin. It was rarely associated with the development of hepatobiliary or other abnormalities. Baseline elevations of liver biochemistry parameters, including any grade of total bilirubin, transaminase or alkaline phosphatase elevations, did not correlate with hyperbilirubinemia during treatment with capecitabine. Hepatobiliary abnormalities resulted in treatment discontinuation in only two patients receiving capecitabine (0.3%) and four patients receiving 5-FU/leucovorin (0.7%).

Only four patients (0.7%) in the capecitabine safety population of 596 patients developed a grade 3 or 4 increase in serum creatinine concentrations during treatment, and in all four this increase was associated with mechanical obstruction of the urinary tract. There was, therefore, no evidence of a direct nephrotoxic effect of capecitabine.

Dose modification and its impact on safety

The median duration of treatment was 4.5 months (range 0.0–16.6 months) in the capecitabine group and 4.6 months (range 0.1–11.9 months) in the 5-FU/leucovorin arm. Fewer patients in the capecitabine group required dose modification for adverse events than in the 5-FU/leucovorin group (33.9% compared with 42.2%; P = 0.0037) (Table 5). In addition, dose modifications for toxicities occurred later in the capecitabine group than in the 5-FU/leucovorin group. The median time to first-level dose reduction (reduction to 75% of the baseline capecitabine dose or 70–80% of baseline 5-FU dose) was 2.5 months in the capecitabine group compared with 1.2 months in the 5-FU/leucovorin group. The median time to second-level dose reduction (reduction to 50% of the baseline capecitabine dose or 49–64% of baseline 5-FU/leucovorin dose) was 3.6 months in the capecitabine group and 3.2 months in the 5-FU/leucovorin group. The baseline demographic characteristics of the patients requiring capecitabine dose modification were similar to those of patients not requiring dose modification for adverse events.

The relationship between safety and systemic exposure [area under the time compared with concentration curve (AUC) and maximum plasma concentration (C_{max})] to key capecitabine metabolites was analyzed in a subpopulation of 481 patients in the capecitabine arm for whom pharmacokinetic data were available. There was broad and consistent overlap in the pharmacokinetic parameters (AUC and C_{max}) of 5′-deoxy-5-fluorocytidine, 5′-DFUR, 5-FU and FBAL in patients who did and did not experience adverse events. Plasma FBAL concentration did not correlate with occurrence or severity of hand–foot syndrome.

The adverse events most commonly leading to treatment interruption or dose reduction were hand–foot syndrome (182 patients) and diarrhea (96 patients) in the capecitabine group, and stomatitis (135 patients) and diarrhea (91 patients) in the 5-FU/leucovorin group. The capecitabine dose-modification scheme was effective in managing the three key adverse events characteristics of infused fluoropyrimidines (diarrhea, hand–foot syndrome and stomatitis). Following dose reduction for diarrhea (89 patients), 14 patients experienced further grade 2 and seven patients experienced further grade 3 or 4 diarrhea (Figure 2A). Following dose reduction for hand–foot syndrome (138 patients), 25 patients experienced a grade 2

Table 5. Incidence of dose reduction in the safety population (n = 1189)

	Capecitabine (n = 596)	5-Fluorouracil (5-FU)/leucovorin (n = 593)
Any dose reduction		
No. of patients (%)	202 (33.9)	250 (42.2)
Dose reduction: first level[a]		
No. of patients (%)	174 (29.2)	245 (41.3)
Median time to reduction (months) (range)	2.5 (0.3–10.2)	1.2 (0.1–9.4)
Dose reduction: second level[b]		
No. of patients (%)	73 (12.2)	33 (5.6)
Median time to reduction (months) (range)	3.6 (0.2–10.4)	3.2 (0.9–8.5)

[a]Represents reduction to 75% of baseline capecitabine dose or 70–80% of preceding 5-FU dose; includes patients with first level reduction and subsequent second level reduction (45 patients with capecitabine and 28 patients with 5-FU/leucovorin), as well as patients withdrawn owing to adverse events.
[b]Represents reduction to 50% of baseline capecitabine dose or 49–64% of baseline 5-FU dose.

recurrence and 20 patients experienced a grade 3 recurrence (Figure 2B). None of the patients receiving capecitabine experienced grade 4 stomatitis; following dose modification for grade 2 or 3 stomatitis (30 patients), there was no further grade 3 stomatitis and six patients (20%) experienced a grade 2 recurrence (Figure 2C).

Impact of dose modification on efficacy

All patients in the capecitabine arm started treatment at the standard dose of 1250 mg/m^2 twice daily. In a time-dependent Cox regression analysis conducted to investigate the impact of dose modification on efficacy, with the onset of first dose modification as a time-dependent co-factor, there was no increase in risk of disease progression (or death in patients with no evidence of disease progression) after the first dose modification (Table 6). There was no increase in the hazard ratio (HR) for the patients treated with capecitabine who required a reduction to either 75% or 50% of the baseline dose for adverse events (HR = 0.97; P = 0.78), and only a minor increase in HR for capecitabine patients requiring dose reductions for adverse events to 50% of baseline dose (HR = 1.06; P = 0.67). Similar analysis in the 5-FU/leucovorin group demonstrated a moderate, but not statistically significant, increase in the risk of disease progression or death for patients receiving 5-FU/leucovorin who required any dose reduction (HR = 1.12; P = 0.22). There was a 30% increase (not statistically significant) in the risk of disease progression or death in patients receiving 5-FU/leucovorin who required dose reduction to 49–64% of baseline 5-FU dose (HR = 1.30; P = 0.19).

Other efficacy parameters, such as response rate and survival, were also investigated, but the data were insufficient for an objective assessment of the impact of dose modification. As responses usually occur early in the treatment course, they depend primarily on the doses given in the first cycles. However, dose reductions tended to occur later (particularly in the capecitabine group, where median onset was day 76), so the impact of dose modification on tumor response was probably quite limited. By contrast, analysis of another important efficacy endpoint, survival, led to substantial modeling issues in a time-dependent Cox model.

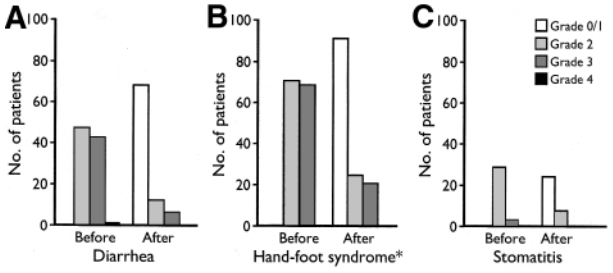

Figure 2.. Impact of capecitabine dose modification on the severity and incidence of treatment-related adverse events: (A) diarrhea, (B) hand–foot syndrome and (C) stomatitis. Asterisk indicates grade 4 not applicable.

Table 6. Impact of dose modification on the risk of disease progression or death

	Hazard ratio	95% Confidence interval	P value (log-rank test)
Capecitabine			
All reductions	0.97	0.80–1.18	0.78
Level 2 reductions[a]	1.06	0.80–1.42	0.67
5-Fluorouracil/leucovorin			
All reductions	1.12	0.94–1.33	0.22
Level 2 reductions[b]	1.30	0.88–1.93	0.19

[a]50% of the baseline dose.
[b]49–64% of baseline dose.

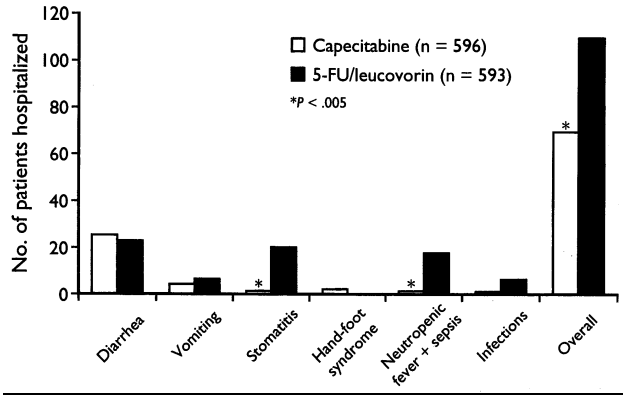

Figure 3. Hospitalizations of patients receiving capecitabine or 5-fluorouracil (5-FU)/leucovorin for key treatment-related adverse events.

Hospitalizations and treatment withdrawals

Hospitalizations for treatment-related adverse events were significantly less common in patients treated with capecitabine compared with 5-FU/leucovorin (11.6% compared with 18.0%, respectively; P <0.005). Overall, there were 76 hospitalizations for treatment-related adverse events in the capecitabine group compared with 113 hospitalizations for treatment-related adverse events with 5-FU/leucovorin. Hospitalization for stomatitis (one case compared with 21 cases) and neutropenic fever/sepsis (one case compared with 17 cases) was significantly less common in patients receiving capecitabine (Figure 3). In the capecitabine group, only two patients required hospitalization for hand–foot syndrome, for <24 h in one patient and <8 h in the other.

In the capecitabine group, 9.6% of patients discontinued treatment because of treatment-related adverse events compared with 6.7% of patients in the 5-FU/leucovorin group (not statistically significant). The main treatment-related adverse events, either alone or in combination, leading to withdrawal from the study were diarrhea (2.7%) and hand–foot syndrome (1.7%) in the capecitabine group, and stomatitis (2.2%) and diarrhea (1.7%) in the 5-FU/leucovorin group.

Impact of baseline renal function on safety

The distribution of patients with renal impairment at baseline, calculated according to the formula of Cockroft and Gault [10], was similar in the two treatment arms (Table 7). Since all patients had a baseline serum creatinine value <1.5 × upper normal limit, in accordance with the study inclusion criteria, the principal factors contributing to impaired calculated creatinine clearance were older age, lower body weight and borderline serum creatinine. Approximately 45% of patients had normal renal function (defined as calculated creatinine clearance >80 ml/min) at baseline, a further 45% had mild renal impairment (creatinine clearance 51–80 ml/min) and only 10% had moderate renal impairment (creatinine clearance 30–50 ml/min). In both the capecitabine and the 5-FU/leucovorin treatment arms, the incidence of grade 3 or 4 adverse events was higher in patients with moderate renal impairment (creatinine clearance 30–50 ml/min) than in those with normal renal function. Among patients receiving capecitabine, the incidence of dose reduction was 44% in those with moderate renal impairment compared with 32% and 33% in patients with mildly impaired and normal renal function,

Table 7. Safety in patient subpopulations grouped according to baseline renal function (calculated creatinine clearance)

	Capecitabine at creatinine clearance rate (ml/min)				5-Fluorouracil/leucovorin at creatinine clearance rate (ml/min)			
	<30	30–50	51–80	>80	<30	30–50	51–80	>80
No. of patients	5	59	257	268	0	61	265	261
Median age	79	74	67	58	–	73	66	58
Median duration of treatment (months)	1.6	4.1	4.6	4.8	–	2.9	4.3	3.8
Incidence of grade 3 or 4 treatment-related adverse events (%)	40	54	41	36	–	51	35	31
Grade 3 or 4 diarrhea (%)	20.0	15.3	13.6	12.3	–	11.5	14.0	10.7
Grade 3 or 4 stomatitis (%)	0	1.7	2.7	1.5	–	26.2	15.5	10.7
Grade 3 hand–foot syndrome (%)	0	25.4	18.3	14.6	–	0	0.8	0.4
Incidence of grade 4 adverse events (%)	40	7	3	1	–	10	5	4
Incidence of treatment withdrawals (%)[a]	20	25	21	10	–	30	14	11
Incidence of dose reductions (%)	40	44	32	33	–	52	40	41
Median time to 25% dose reduction (months)	1.6	2.8	2.2	2.8	–	1.2	1.0	1.2
Median time to 50% dose reduction (months)	2.1	3.0	3.7	3.9	–	3.1	2.8	3.7
Response rate (%)[b]	40	24	27	25	–	10	19	16

[a]Due to any adverse event, laboratory abnormality or death.
[b]Complete or partial response, investigator assessed.

Table 8. Safety in capecitabine patient subpopulations grouped according to age

	All	Age (years)							
		<50	50–54	55–59	60–64	65–69	70–74	75–79	≥80
No. of patients	596	72	69	82	85	124	100	51	13
Incidence of grade 3 or 4 treatment-related adverse events (%)	40	31	32	43	34	40	49	41	69
Grade 3 or 4 diarrhea (%)	13	4	13	17	14	13	14	12	31
Grade 3 or 4 stomatitis (%)	2	1	1	0	2	4	3	0	8
Grade 3 hand–foot syndrome (%)	17	15	12	17	11	16	22	31	15
Incidence of grade 4 adverse events (%)	3	0	1	1	4	5	4	2	15

respectively (Table 7). More patients with moderate renal impairment were withdrawn from capecitabine therapy (not significant), with most withdrawals occurring in the first two treatment cycles. The principal cause of treatment withdrawal was diarrhea. In patients with mild renal impairment at baseline, capecitabine at its standard starting dose showed an acceptable tolerability profile. Dose recommendations based on creatinine clearance at baseline are presented in the Discussion.

The general trends seen between subpopulations grouped according to baseline renal function in the capecitabine group were also seen in the 5-FU/leucovorin group, but were more pronounced in the 5-FU/leucovorin group. In patients receiving 5-FU/leucovorin, the incidence of grade 3 or 4 adverse events was higher in the 61 patients with moderately impaired creatinine clearance than in those with normal renal function (grade 3 or 4: 51% compared with 31%; grade 4, 10% compared with 4%, respectively). There was a particularly high increase in the frequency of grade 3 or 4 stomatitis in patients treated with 5-FU/leucovorin with moderate renal impairment at baseline (26% compared with 11% of patients with normal renal function). The median duration of treatment was also shorter in patients with moderate renal impairment (2.9 months compared with 3.8 months in those with normal renal function). The incidence of treatment withdrawals from 5-FU/leucovorin was 30% in patients with moderate renal impairment compared with 11% in the subgroup of patients with normal renal function. More than half (52%) of the patients in the 5-FU/leucovorin group with moderate renal impairment required dose reduction for adverse events.

The objective response rate to capecitabine in the subgroup of patients with moderately impaired renal function (24%) was similar to that achieved in patients with normal or mildly impaired renal function (25% and 27%, respectively) (Table 7). In contrast, response rates in patients with moderately impaired renal function receiving 5-FU/leucovorin were lower (10%) than in patients with normal or mildly impaired renal function (16% and 19%, respectively), indicating that the efficacy of 5-FU/leucovorin was reduced in patients with moderate renal impairment.

Impact of age on the safety profile of capecitabine

The data from the retrospective analysis indicated that in patients with moderately impaired creatinine clearance at baseline there was an increased risk of toxicity. Since one of the most important factors influencing creatinine clearance is age, a further subpopulation analysis was conducted, grouping patients in 5-year age categories. The safety results for capecitabine according to age are shown in Table 8. There was an increased incidence of grade 3 or 4 adverse events, particularly gastrointestinal toxicities, in patients aged 80 years or older receiving capecitabine, whereas differences were modest in the younger age categories. Since age and renal function are strongly correlated, Cox regression analyses were performed to further investigate the relationship between age, baseline creatinine clearance and the safety profile of capecitabine. A univariate Cox regression analysis demonstrated that both age ($P = 0.04$) and creatinine clearance ($P = 0.05$) have a statistically significant impact on the safety profile of capecitabine. However, a multivariate Cox regression analysis adjusting for creatinine clearance showed that age does not have an additional, statistically significant, independent im-pact ($P = 0.72$) on the safety profile of capecitabine. This analysis indicates that the less favorable safety profile of capecitabine in older patients is due primarily to age-related impairment of renal function.

Discussion

The integrated analysis of the two phase III studies in metastatic colorectal cancer confirmed the results of the individual trials [7, 8]. It confirms that as first-line therapy, capecitabine achieves a superior response rate, equivalent survival and equivalent time to disease progression compared with 5-FU/leucovorin [9]. Results of the integrated analysis also confirmed that the safety profile of capecitabine was favorable compared with that of 5-FU/leucovorin, as demonstrated by a significantly lower incidence of diarrhea, stomatitis, nausea and alopecia. The incidence of grade 3 or 4 neutropenia was also lower than with 5-FU/leucovorin, leading to significantly fewer neutropenic fever/sepsis cases and associated hospitalizations. The most frequently occurring toxicities in the capecitabine

group were hand–foot syndrome and diarrhea. Overall, significantly fewer patients treated with capecitabine required hospitalization for adverse events compared with patients receiving 5-FU/leucovorin.

Capecitabine at its recommended dose of 1250 mg/m^2 twice daily on days 1–14 followed by a 7-day rest period was well tolerated and the majority of patients (66%) did not require dose modification. Furthermore, the lower incidence and later onset of adverse events requiring dose modification with capecitabine indicate that patients receiving capecitabine who experience disease progression early in the treatment period are more likely to be spared unnecessary toxicity than patients receiving 5-FU/leucovorin.

In patients requiring dose modification, the full dose of capecitabine was administered for a median of 11 weeks before the first dose modification. In contrast, there was a significantly higher incidence of dose modification in the 5-FU/leucovorin group, and patients requiring dose modification received a median of only 5 weeks of therapy at the full dose of 5-FU/leucovorin. As capecitabine is an oral agent, the dose can be titrated at the first appearance of a moderate toxicity, thus reducing the likelihood of development of more serious toxicities. Furthermore, the twice-daily dosing schedule provides numerous opportunities per cycle to interrupt therapy or reduce the dose after administration of the first dose. Analyses of the integrated data from the phase III trials in colorectal cancer have confirmed that the capecitabine dose-modification scheme is a key component of the treatment regimen, and was effective in preventing the recurrence of severe toxicities during the treatment period.

Most importantly, the efficacy of capecitabine was maintained in patients requiring dose modification. All patients started treatment at the full standard starting dose and, where needed, doses were adjusted to the individual's tolerable dose. There was no increase in the risk of disease progression or death in capecitabine-treated patients requiring dose modification for adverse events compared with those who did not require dose modification. However, the risk of disease progression following dose reduction in the 5-FU/leucovorin group was increased by 12%, and by 30% in patients requiring a second-level dose reduction (not statistically significant).

In a retrospectively conducted subpopulation analysis of the safety data according to calculated creatinine clearance, the safety profile in the subpopulation of patients with moderate renal impairment at baseline was quantitatively different from that seen in patients with normal renal function. There were more adverse events, particularly during the early stages of treatment, leading to more dose reductions. This effect was seen in both treatment arms.

The results of the subpopulation safety analysis suggested that in patients with moderately impaired renal function, a reduced starting dose may be prudent. Consequently, data from an additional pharmacokinetic trial of capecitabine in patients with solid tumors were analyzed to identify the most appropriate starting dose of capecitabine for these patients [11]. This study included patients with normal renal function and patients with mild, moderate or severe renal impairment. Unlike the phase III clinical trials, serum creatinine >1.5 × upper normal limit at baseline did not preclude inclusion in the study. The results indicated that baseline creatinine clearance had no effect on the pharmacokinetics of intact drug and 5-FU. However, moderate impairment of creatinine clearance increased the AUC of the key metabolite 5′-DFUR, the immediate precursor to 5-FU, by 35% compared with the subgroup of patients with normal renal function. This increase in systemic exposure to 5′-DFUR may explain the increased incidence of clinically relevant adverse events in patients with moderate renal impairment at baselines because 5′-DFUR plasma concentrations reflect the tissue exposure to 5-FU most closely. These pharmacokinetic findings, together with the safety analysis of the clinical database, support the recommendation that in patients with moderate renal impairment, the starting dose should be reduced to 75% of the standard starting dose, thus aiming for similar systemic exposure in patients with moderate renal impairment as in patients with normal renal function receiving the standard starting dose. Furthermore, data from the pharmacokinetic study showed that in patients with severe renal impairment, the toxicity profile of capecitabine was even more pronounced. This led to a contra-indication for capecitabine in patients with severe renal impairment at baseline. However, there was no evidence of direct nephrotoxicity with capecitabine.

It is important to note that patients with moderate renal impairment currently do not have a safer treatment option than capecitabine, as in the present study 5-FU/leucovorin resulted in an increase in toxicity of a similar or higher magnitude. There was a higher incidence of grade 3 or 4 treatment-related adverse events, and the incidence of stomatitis was almost doubled in patients with moderate renal impairment who received 5-FU/leucovorin. More than half of the patients with moderate renal impairment required 5-FU dose reduction. Furthermore, efficacy was substantially reduced in these patients. In contrast, response rates to capecitabine were similar in subgroups of patients with moderately impaired, mildly impaired or normal renal function. It is likely that, as with capecitabine and 5-FU/leucovorin, other oral fluoropyrimidines will show more pronounced toxicities in patients with moderate renal impairment. The increased exposure to 5-FU in patients with moderate renal impairment treated with eniluracil, and the associated increase in toxicity, led to the initiation of a number of trials investigating lower starting doses of eniluracil in patients with moderate renal impairment [12]. Patients with severe renal impairment may be ineligible for treatment with other oral fluoropyrimidines.

In patients with mild renal impairment at baseline, the safety profile was similar to that observed in patients with normal renal function. Therefore in these patients capecitabine treatment should be initiated at the standard dose (1250 mg/m^2 twice daily). Careful monitoring is advised, with prompt treatment interruption and dose reduction in the event of a grade 2

or higher toxicity, as detailed in the standard capecitabine dose-modification scheme.

Creatinine clearance and age are highly correlated, and therefore the safety data from the phase III colorectal cancer trials were analyzed according to 5-year age intervals. The safety profile of capecitabine was found to be notably poorer in patients aged over 80 years, with a higher incidence of grade 3 or 4 gastrointestinal events. However, a multivariate Cox regression analysis demonstrated that age did not have an additional, statistically significant impact on the safety profile of capecitabine over and above creatinine clearance. It was concluded, therefore, that the decreased tolerability of capecitabine in older patients was caused primarily by an age-related decline in renal function, as evident from calculated creatinine clearance, whereas serum creatinine was still within normal limits.

Another pharmacokinetic study showed that in patients with mild to moderate hepatic dysfunction at baseline due to liver metastases, both the $AUC_{0-\infty}$ and C_{max} of capecitabine were increased by 50% compared with values for patients with normal hepatic function [13]. However, there were no significant differences in the pharmacokinetic parameters of the main capecitabine metabolites (5′-DFUR, 5-FU and FBAL) between the patient groups. It was concluded, therefore, that there is no need for a priori adjustment of the dose in patients with mild to moderate hepatic dysfunction, although caution should be exercised when administering capecitabine to these patients.

Capecitabine has a number of features that potentially contribute to its favorable safety profile. Its unique mechanism of activation results in the generation of 5-FU preferentially in tumor tissue, minimizing systemic exposure to 5-FU [3]. In addition the chemical structure of capecitabine prevents direct release of 5-FU into the gastrointestinal tract. The data from the phase III trials in patients with colorectal cancer confirm that the standard starting dose of capecitabine (1250 mg/m^2 twice daily, days 1–14 followed by a 7-day rest period) is well tolerated by the majority of patients. Based on these data and analysis of the pharmacokinetic trial in patients with impaired renal function at baseline, a lower starting dose (950 mg/m^2 twice daily, days 1–14 followed by a 7-day rest period) is recommended for patients with moderate renal impairment (baseline creatinine clearance 30–50 ml/min, calculated according to the formula of Cockroft and Gault [10]).

Patient education is essential for anyone receiving cytotoxic chemotherapy in an outpatient setting. Patients receiving capecitabine should be educated to recognize side-effects and their severity. It is important that patients interrupt treatment upon the development of a moderate or more severe toxicity, and, if necessary, contact their physician or nurse for further advice. Patients should be reassured that efficacy will not be compromised if treatment is interrupted or modified, since patients may otherwise be reluctant to report adverse events and risk treatment interruption. This is partly because of a fear that efficacy may be reduced if treatment is interrupted or the dose is reduced. Patient follow-up procedures can help to ensure optimal management of adverse events, particularly in patients receiving capecitabine for the first time.

Capecitabine is a convenient, effective and well-tolerated agent for the treatment of patients with breast and colorectal cancer. For these indications, capecitabine provides a valuable outpatient treatment option. These analyses have shown that the current capecitabine dose-modification scheme is effective in the management of adverse events. Future trials will investigate the impact of capecitabine dose reduction to 75% of the baseline dose at the first occurrence of a grade 2 toxicity, which may further improve the safety profile of capecitabine.

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