Original article

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Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial

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Background: Oral capecitabine achieves a superior response rate with an improved safety profile compared with bolus 5-fluorouracil–leucovorin (5-FU/LV) as first-line treatment for patients with metastatic colorectal cancer. We report here the results of a large phase III trial investigating adjuvant oral capecitabine compared with 5-FU/LV (Mayo Clinic regimen) in Dukes' C colon cancer.

Patients and methods: Patients aged 18–75 years with resected Dukes' C colon carcinoma were randomized to receive 24 weeks of treatment with either oral capecitabine 1250 mg/m^2 twice daily, days 1–14 every 21 days (n = 993), or i.v. bolus 5-FU 425 mg/m^2 with i.v. leucovorin 20 mg/m^2 on days 1–5, repeated every 28 days (n = 974).

Results: Patients receiving capecitabine experienced significantly (P <0.001) less diarrhea, stomatitis, nausea/vomiting, alopecia and neutropenia, but more hand–foot syndrome than those receiving 5-FU/LV. Fewer patients receiving capecitabine experienced grade 3 or 4 neutropenia, febrile neutropenia/sepsis and stomatitis (P <0.001), although more experienced grade 3 hand–foot syndrome than those treated with 5-FU/LV (P <0.001). Capecitabine demonstrates a similar, favorable safety profile in patients aged <65 years or ≥65 years old.

Conclusions: Based on its improved safety profile, capecitabine has the potential to replace 5-FU/LV as standard adjuvant treatment for patients with colon cancer. Efficacy results are expected to be available in 2004.

Keywords: Adjuvant treatment, capecitabine, chemotherapy, colorectal cancer

Introduction

Clinical trials have demonstrated that adjuvant treatment improves outcomes for patients with resected colon cancer. A pooled analysis of three studies (including 1493 patients) confirmed that adjuvant treatment with 5-fluorouracil (5-FU) plus leucovorin (LV) significantly increased 3-year event-free survival and overall survival, leading to a 22% reduction in mortality (P = 0.029) compared with no treatment [1]. In addition, a recent phase III trial confirmed that 5-FU/LV (Mayo Clinic regimen) is a more effective adjuvant treatment than 5-FU/levamisole, significantly reducing recurrence and achieving superior disease-free and overall survival [2]. Currently, it is accepted that treatment with 5-FU/LV for 6–8 months is the standard adjuvant therapy for Dukes' C (stage III) colon cancer, with trials showing no difference in the efficacy of weekly and monthly 5-FU/LV regimens [3, 4]. Infusional 5-FU/LV is not standard for adjuvant treatment of colon cancer. The one trial comparing bolus with infusional 5-FU/LV failed to show non-inferiority [5].

Despite the advances afforded by the use of 5-FU/LV, evidence suggests that there is considerable discrepancy between consensus recommendations advocating the routine use of adjuvant treatment and its use in the community [6]. In particular, older patients are less likely to receive chemotherapy, possibly due to physicians' concerns about increased toxicity in this group. In a German randomized trial comparing 5-FU/LV with 5-FU/levamisole as

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adjuvant treatment for resected stage III colon cancer, treatment was prematurely discontinued in 24% of patients, primarily due to toxicity and lack of compliance [7]. Better-tolerated, more convenient and more active chemotherapy is required for the adjuvant treatment of colon cancer.

In the metastatic setting both a questionnaire-based study [8] and a randomized, treatment cross-over study [9] indicated that the majority of patients (84–89%) prefer oral chemotherapy, as long as efficacy is not compromised. Patients indicated that the principal reasons for this preference were the avoidance of problematic i.v. access and the improved convenience of home-based treatment. In addition, Payne [10] demonstrated that patients' quality of life was significantly improved with home-based compared with hospital-based therapy.

Capecitabine (Xeloda®; F. Hoffmann-La Roche, Basel, Switzerland) is an oral fluoropyrimidine that generates 5-FU preferentially in tumor tissue via a three-step enzymatic cascade. The final step is catalyzed by thymidine phosphorylase, an enzyme with significantly higher activity in tumor compared with healthy tissue [11]. Oral capecitabine is effective in the treatment of metastatic colorectal cancer, offering improved convenience and patient acceptability compared with i.v. 5-FU/LV. Two large phase III trials have shown that, as first-line therapy for metastatic colorectal cancer, capecitabine achieves a superior response rate and at least equivalent time to disease progression (TTP) and overall survival compared with 5-FU/LV (Mayo Clinic regimen) [12]. Capecitabine also demonstrated an improved safety profile compared with 5-FU/LV [13], with significantly less diarrhea, stomatitis, nausea, alopecia and grade 3 or 4 neutropenia, leading to less febrile neutropenia and fewer associated hospitalizations (P <0.001). Hand–foot syndrome occurred more frequently in the capecitabine arm than in the 5-FU/LV arm (P <0.001), but this cutaneous side-effect is never life threatening and can be managed effectively by treatment interruption and/or dose modification [13].

Considering the documented high activity, good tolerability and improved convenience in patients with metastatic disease, capecitabine has been further evaluated as adjuvant therapy for colon cancer. This international, multicenter, randomized, open-label phase III study evaluated capecitabine versus i.v. 5-FU/LV (Mayo Clinic regimen) as adjuvant therapy for patients with Dukes' C colon cancer. The primary objective of the study was to demonstrate that disease-free survival with capecitabine is at least equivalent to that achieved with 5-FU/LV (Mayo Clinic regimen). Secondary end points included overall survival, quality of life, medical resource utilization and safety. The trial has completed recruitment of 1987 patients and efficacy results are expected in 2004. We report here the results of the planned safety analysis, conducted 19 months after the enrollment of the last patient.

Patients and methods

The study was conducted in full concordance with the Declaration of Helsinki and all of its amendments, or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Patients gave full informed consent prior to study-specific screening procedures.

Eligibility criteria

Eligible patients were aged 18–75 years (although some ≥75 years were given waivers to participate in the study) and had histologically confirmed Dukes' C colon carcinoma (with at least one positive lymph node) after surgery with curative intent. Carcinoembryonic antigen (CEA) concentrations were to be within the normal range. Patients were required to have fully recovered following surgery and have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 and a life expectancy of at least 5 years.

Patients with evidence of metastatic disease, including tumor cells in ascites at study entry, were ineligible. Those who had received cytotoxic chemotherapy or who had organ allografts, clinically significant cardiac disease, severe renal impairment or central nervous system disorders were also excluded. Pregnant or lactating women and sexually active patients unwilling to practice contraception were excluded.

Study design and treatment

This international, multicenter, randomized, open-label, parallel-group phase III study was designed to demonstrate that capecitabine achieves at least equivalent disease-free survival to 5-FU/LV (the Mayo Clinic regimen) when administered as adjuvant treatment following surgery for Dukes' stage C colon cancer. Secondary end points were overall survival, quality of life, medical resource utilization and safety profile.

Patients were randomized to receive 24 weeks of treatment with either oral capecitabine 1250 mg/m^2 twice daily, given on days 1–14 every 21 days, or i.v. leucovorin 20 mg/m^2 by rapid infusion followed immediately by i.v. bolus 5-FU 425 mg/m^2, days 1–5 every 28 days.

After inclusion of 1363 patients, an amendment reduced the capecitabine starting dose by 25% in patients with moderate renal impairment (estimated creatinine clearance 30–50 ml/min [14]) based on newly available data [13, 15].

Screening/baseline assessments

Assessments included medical history, a general physical examination, vital signs, physical measurements, performance status, laboratory tests (hematology, blood chemistry, pregnancy test, urinalysis and CEA determination) and ECG. The presence of metastatic disease was excluded by computed tomography (CT) scan or magnetic resonance imaging (MRI) of abdomen and pelvis and chest X-ray. A baseline quality of life assessment (QLQ-C30) was also performed.

Evaluation of safety

This prospectively planned safety analysis was conducted 19 months after enrollment of the last patient. Adverse events were recorded and graded according to National Cancer Institute of Canada common toxicity criteria (NCIC CTC), revised in May 1991. Hand–foot syndrome was graded 1 to 3, as described previously [16, 17]. Laboratory analyses performed at the beginning of each cycle included: hemoglobin, white blood and platelet cell counts, total bilirubin, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, serum creatinine, potassium, sodium, phosphate, uric acid and calcium.

Dose modification

The capecitabine and 5-FU/LV (Mayo Clinic regimen) dose modification schemes have been published in detail [13]. In the 5-FU/LV treatment group, the dose of leucovorin was not modified, but the 5-FU dose was reduced (to 80% or 70% of the preceding dose) or escalated (to 110% of the preceding dose) depending upon the occurrence and severity of either clinical adverse events or hematological/laboratory abnormalities, or their absence in the preceding treatment cycles. In the capecitabine group, treatment was continued at the same dose (without interruption or dose reduction) if patients experienced

Table 1. Patient baseline and disease characteristics

	Capecitabine (n = 993)	5-FU/LV (n = 974)
Male/female (%)	54/46	54/46
Median age, years (range)	62 (25–80)	63 (22–82)
ECOG score: 0/1 (%)	85/15	85/15
Node status: N1/N2 (%)	69/30	71/29
Preoperative CEA values (%)		
Normal	83	85
>1–≤2× ULN	6	5
>2× ULN	2	2
>5× ULN	1	<1
Missing	8	8

5-FU/LV, 5-fluorouracil–leucovorin; ECOG, Eastern Cooperative Oncology Group; N1, metastases in 1–3 regional lymph nodes; N2, metastases in ≥4 regional lymph nodes; CEA, carcinoembryonic antigen; ULN, upper limit of normal.

Table 2. Most common (≥10%) treatment-related adverse events (all grades)

	Percentage of patients		P value
	Capecitabine (n = 993)	5-FU/LV (n = 974)	
Diarrhea	46	64	<0.001
Nausea/vomiting	36	51	<0.001
Stomatitis	22	60	<0.001
Hand–foot syndrome	62	10	<0.001
Fatigue/asthenia	23	23	NS
Alopecia	6	22	<0.001
Abdominal pain	10	13	NS
Lethargy	10	9	NS
Anorexia	9	10	NS

5-FU/LV, 5-fluorouracil–leucovorin; NS, not significant.

toxicities no greater than grade 1 or other toxicities unlikely to become severe or life threatening (e.g. alopecia). All patients were instructed to interrupt capecitabine treatment upon the development of moderate or severe toxicity (grade ≥2), and to immediately contact the clinic for further directions. At a second occurrence of grade 2 toxicity, or after appearance of grade 3 or 4 toxicity, the capecitabine dose was to be reduced by 25%. In the event of further toxicity, a second-step dose reduction to 50% of the starting dose was allowed. Treatment was not resumed until symptoms had resolved to grade 0 or 1. Once the capecitabine or 5-FU/LV dose had been reduced, it was not to be increased at a later time.

Results

Patient population

Between November 1998 and November 2001, 1987 patients (intention-to-treat population) were enrolled in 164 centers worldwide. The safety population included all patients receiving at least one dose of study drug and followed up for safety (n = 1967, comprising 993 patients randomized to capecitabine and 974 patients randomized to 5-FU/LV). The treatment arms were well balanced in terms of baseline prognostic factors (Table 1).

Safety profile

Table 2 lists the most frequent (≥10% of patients) treatment-related adverse events of all grades. Patients receiving capecitabine experienced significantly (P <0.001) less diarrhea (46% versus 64% with 5-FU/LV), nausea/vomiting (36% versus 51%), stomatitis (22% versus 60%) and alopecia (6% versus 22%). In addition, neutropenia, as a clinical adverse event requiring medical intervention, was significantly less common with capecitabine versus 5-FU/LV (2% versus 8%; P <0.001). The only treatment-related adverse event occurring more commonly with capecitabine was hand–foot syndrome (62% versus 10% with 5-FU/LV; P <0.001).

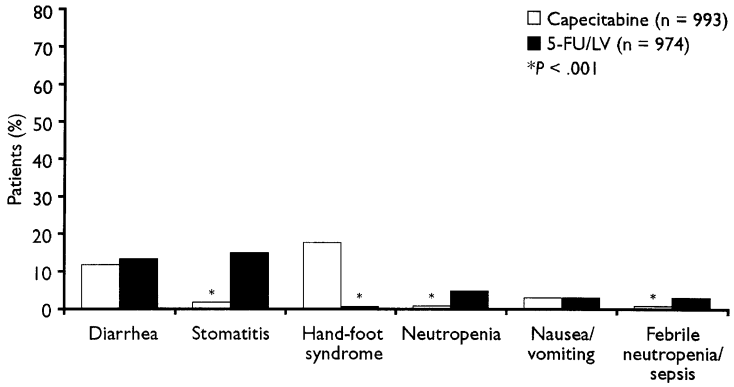

Figure 1. Most common (>2%) treatment-related grade 3/4 adverse events.

Table 3. Incidence of early severe toxicities (i.e. grade 3 or 4 gastrointestinal toxicities, infections, neutropenia, and thrombocytopenia occurring within the first 21 days of treatment)[a]

	Capecitabine		5-FU/LV	
	<65 years (n = 596) (%)	≥65 years (n = 397) (%)	<65 years (n = 562) (%)	≥65 years (n = 412) (%)
Any defined events	4.9	6.3	15.1	19.7
Stomatitis	0.7	1.8	7.7	12.1
Diarrhea	2.3	3.5	6.0	4.6
Neutropenia[b]	1.7	1.0	4.1	9.2
Thrombocytopenia[b]	1.7	1.8	0.2	0.2
Nausea	1.0	0.8	0.5	0.5
Vomiting	0.7	0.3	1.2	0.5
Abdominal pain	0.7	0.5	0.4	1.5
Intestinal obstruction	0.2	0.3	0.4	0.5
Febrile neutropenia	0	0	0.4	1.0
Other toxicities[c]	1.0	2.0	1.2	2.2

[a]An individual patient can have more than one specific grade 3 or 4 event.
[b]Neutropenia and thrombocytopenia recorded as grade 3 or 4 laboratory abnormalities.
[c]Other gastrointestinal toxicities and infections affecting two or less patients in either of the treatment arms.
5-FU/LV, 5-fluorouracil–leucovorin.

Figure 1 shows severe (grade 3 or 4) toxicities. Patients receiving capecitabine experienced significantly less grade 3 or 4 stomatitis (2% versus 14% with 5-FU/LV; P <0.001) and grade 3 or 4 neutropenia requiring medical intervention (0.6% versus 5%; P <0.001). Febrile neutropenia/sepsis was also significantly less common in patients receiving capecitabine (0.3% versus 3%; P <0.001). As expected, grade 3 hand–foot syndrome was significantly more common in the capecitabine arm (18% versus 0.6%; P <0.001).

Early, severe (grade 3 or 4) fluoropyrimidine-related toxicities, defined as the most clinically relevant types of adverse events (i.e. gastrointestinal toxicities, infections, neutropenia and thrombocytopenia) occurring within the first 21 days of treatment are shown in Table 3. Overall, significantly fewer patients receiving capecitabine experienced early severe toxicities than patients receiving 5-FU/LV (5.4% versus 17%, respectively; P <0.001). Patients receiving 5-FU/LV also experienced more early grade 3 or 4 stomatitis (10% versus 1%), diarrhea (5% versus 3%) and neutropenia (6% versus 1%) than those receiving capecitabine.

Laboratory abnormalities

Table 4 lists the most commonly occurring grade 3 or 4 laboratory abnormalities in each treatment arm. Grade 3 or 4 neutropenia (as a laboratory abnormality) was significantly less common in the capecitabine arm compared with the 5-FU/LV arm (2% versus 26%; P <0.001). Also, the overall incidence of neutropenia (all grades) was significantly lower in the capecitabine arm versus the 5-FU/LV arm (31% versus 61%; P <0.001). Grade 3 hyperbilirubinemia [defined as elevated bilirubin concentrations ≤3 times the upper limit of normal (ULN)] was more common with capecitabine

Table 4. Most frequently occurring (≥3%) grade 3 or 4 laboratory abnormalities

	Percentage of patients		*P* value
	Capecitabine (n = 993)	5-FU/LV (n = 974)	
Hyperbilirubinemia	20	6	<0.001
Lymphocytopenia	13	13	NS
Neutropenia	2	26	<0.001
Leucopenia	1	5	<0.001

5-FU/LV, 5-fluorouracil–leucovorin; NS, not significant.

Table 5. Incidence of most common (≥10%) treatment-related adverse events (all grades) according to age

	Capecitabine		5-FU/LV	
	<65 years (n = 596) (%)	≥65 years (n = 397) (%)	<65 years (n = 562) (%)	≥65 years (n = 412) (%)
Diarrhea	42	52	65	63
Stomatitis	19	27	59	62
Nausea	32	34	44	49
Vomiting	13	16	18	21
Hand–foot syndrome	61	63	9	11
Fatigue	13	17	15	15
Abdominal pain	9	12	13	13
Neutropenia	2	3	10	7

5-FU/LV, 5-fluorouracil–leucovorin.

Table 6. Analyses of most common (>2%) grade 3 or 4 adverse events by age group

	Capecitabine		5-FU/LV	
	<65 years (n = 596) (%)	≥65 years (n = 397) (%)	<65 years (n = 562) (%)	≥65 years (n = 412) (%)
Diarrhea	10	13	13	13
Stomatitis	1	3	11	18
Hand–foot syndrome	16	20	<1	<1
Neutropenia[a]	2	3	26	27
Nausea	2	1	2	1
Vomiting	2	1	2	2

[a]Neutropenia as a grade 3 or 4 laboratory abnormality.
5-FU/LV, 5-fluorouracil–leucovorin.

(18.6% versus 5.9%). Similarly, grade 4 hyperbilirubinemia (defined as elevated bilirubin concentrations >3 times ULN) was more common with capecitabine (1.4% versus 0.3%; P <0.001). The incidence of grade 3 or 4 abnormalities in ASAT and ALAT in both treatment arms was, however, low (0.7% and 1.6%, respectively, with capecitabine; and 0.3% and 0.6%, respectively, with 5-FU/LV).

Impact of age on safety profile

The safety profile of capecitabine and 5-FU/LV were analyzed in patients aged <65 and ≥65 years (Tables 5 and 6). Overall, capecitabine showed a more favorable safety profile than 5-FU/LV in both the younger and older patients, with less treatment-related diarrhea, nausea, vomiting, stomatitis and neutropenia, but more hand–foot syndrome (Table 5). For grade 3 or 4 adverse events, patients aged <65 and ≥65 years receiving capecitabine experienced less stomatitis and neutropenia, and more hand–foot syndrome compared with the 5-FU/LV-treated patients (Table 6).

Older patients (≥65 years) receiving 5-FU/LV experienced a higher incidence of early severe toxicities (gastrointestinal toxicities, infections, neutropenia and thrombocytopenia) during the first 21 days of treatment compared with the younger patients (<65 years) (20% versus 15%, respectively) (Table 3). In contrast,

Table 7. Adverse events commonly leading to treatment modification

	Treatment modification[a]		Treatment discontinuation	
	Capecitabine (n = 993) (%)	5-FU/LV (n = 974) (%)	Capecitabine (n = 993) (%)	5-FU/LV (n = 974) (%)
Diarrhea	15	19	3	3
Hand–foot syndrome	31	<1	3	<1
Stomatitis	3	23	<1	2
Neutropenia	3	13	0	<1

[a]Both dose reductions and treatment interruptions included.
5-FU/LV, 5-fluorouracil–leucovorin.

Table 8. Number of patients starting each cycle

	Capecitabine (n = 993) [n (%)]	5-FU/LV[a] (n = 974) [n (%)]
Cycle 1	993 (100)	974 (100)
Cycle 2	965 (97)	936 (96)
Cycle 3	935 (94)	913 (94)
Cycle 4	920 (93)	894 (92)
Cycle 5	901 (91)	880 (90)
Cycle 6	886 (89)	862 (89)
Cycle 7	868 (87)	–
Cycle 8	833 (84)	–

[a]Mayo Clinic regimen arm included six cycles of treatment.
5-FU/LV, 5-fluorouracil–leucovorin.

with capecitabine the incidence of early severe toxicities was similar in patients aged ≥65 years and <65 years (4.9% versus 6.3%, respectively).

Dose modification and premature withdrawal

Dose reduction was required in 42% of patients receiving capecitabine compared with 44% of patients receiving 5-FU/LV. Median time to first dose reduction was longer for patients receiving capecitabine compared with 5-FU/LV (78 versus 41 days). Second-level dose reductions (to <60% of the capecitabine starting dose and <75% of the 5-FU/LV starting dose) were also more common in the 5-FU/LV arm than the capecitabine arm (26% versus 13%); median time to second-level dose reduction was longer for patients receiving capecitabine (113 versus 57 days with 5-FU/LV).

The adverse events most commonly leading to dose modification (including treatment interruption and dose reduction) were hand–foot syndrome (31%) and diarrhea (15%) in the capecitabine arm, and stomatitis (23%) and diarrhea (19%) in the 5-FU/LV arm (Table 7).

Premature withdrawal was infrequent in both treatment arms. In total, 84% of patients receiving capecitabine completed all eight cycles of treatment (24 weeks) and 88% of patients on 5-FU/LV received all six cycles (24 weeks). Table 8 shows the number of patients starting each cycle of treatment. Premature withdrawal due to adverse events occurred in 12% of patients receiving capecitabine and 8% of those receiving 5-FU/LV.

There were three (0.3%) treatment-related deaths in the capecitabine arm, two patients aged <65 years (one due to multi-organ failure on day 23, the other due to septic shock on day 22) and one patient aged ≥65 years (due to pneumonia on day 91). There were four deaths (0.4%) in the 5-FU/LV treatment arm, three patients aged <65 years (one on day 16 after experiencing severe diarrhea and vomiting, one due to respiratory arrest on day 69, and one due to gastrointestinal hemorrhage on day 131) and one patient aged ≥65 years (due to bronchopneumonia on day 189). Overall, there was a low incidence of all-cause, 60-day mortality, with five deaths in the capecitabine arm (0.5%) and four in the 5-FU/LV arm (0.4%).

Resource use: treatments for adverse events

Fewer patients receiving capecitabine required medications for the treatment of adverse events (703 patients versus 768 patients with 5-FU/LV). The most commonly prescribed treatments for adverse events were loperamide, antibiotics and metoclopramide (Table 9). Fewer patients receiving capecitabine required loperamide (231 versus 372 with 5-FU/LV) and metoclopramide (141 versus 243 with 5-FU/LV), reflecting the significantly lower incidences of diarrhea and nausea/vomiting in the capecitabine

Table 9. Most frequently (≥10% of patients) administered treatments for adverse events

	No. of patients (%)	
	Capecitabine (n = 993)	5-FU/LV (n = 974)
Loperamide	231 (23)	372 (38)
Antibiotics	217 (22)	289 (30)
Metoclopramide	141 (14)	243 (25)
Paracetamol	97 (10)	107 (11)
Pyridoxine	152 (15)	20 (2)
Benzydamine[a]	25 (3)	108 (11)

[a]Benzydamine is a mouthwash/spray for painful inflammatory conditions of oropharynx.
5-FU/LV, 5-fluorouracil–leucovorin.

group. Fewer patients receiving capecitabine required treatment with antibiotics (217 versus 289 with 5-FU/LV). The lower incidence of neutropenia with capecitabine was reflected by less frequent need for granulocyte colony-stimulating factor (G-CSF). Seven patients receiving capecitabine required G-CSF compared with 27 in the 5-FU/LV group.

Discussion

Capecitabine is a firmly established first-line treatment for metastatic colorectal cancer, based on its superior antitumor activity and improved safety profile compared with i.v. 5-FU/LV [12]. In light of the improved convenience and patient acceptability of oral capecitabine, the current study is being conducted to determine whether capecitabine can replace i.v. 5-FU/LV as the standard adjuvant treatment for Dukes' C colon cancer. Efficacy data are not expected until 2004, but the results of this planned safety analysis demonstrate that capecitabine has an improved safety profile in the adjuvant setting compared with bolus i.v. 5-FU/LV. Furthermore, the improved safety profile of capecitabine in the adjuvant setting mirrors that observed in the metastatic setting [13].

As first-line treatment for metastatic colorectal cancer, capecitabine was associated with significantly lower incidences of diarrhea, stomatitis, nausea, alopecia, neutropenia (including grade 3 or 4) and febrile neutropenia/sepsis compared with 5-FU/LV (Mayo Clinic regimen). Hand–foot syndrome occurred more frequently with capecitabine. The improved safety profile of adjuvant capecitabine versus 5-FU/LV is demonstrated by significantly lower incidences of diarrhea, nausea/vomiting, stomatitis (including grade 3 or 4), alopecia, neutropenia (including grade 3 or 4) and febrile neutropenia/sepsis. The most common treatment-related adverse event with adjuvant capecitabine is a cutaneous side effect, hand–foot syndrome. Experience in the metastatic setting shows that hand–foot syndrome is effectively managed by adequate patient education, treatment interruption and, if necessary, dose reduction, and rarely leads to treatment discontinuation or hospitalization [13]. Hyperbilirubinemia is a known side effect of oral fluoropyrimidines and rarely associated with clinical abnormalities [13]. Grade 3 or 4 hyperbilirubinemia was more common in patients receiving capecitabine than in those receiving 5-FU/LV. But elevated ASAT and ALAT concentrations were uncommon in both treatment arms, suggesting that hyperbilirubinemia is not associated with hepatobiliary dysfunction.

A low level of early severe toxicities, potentially leading to treatment discontinuation or even death, is particularly important in the adjuvant setting. In this study, patients receiving capecitabine were three times less likely to experience severe early gastrointestinal toxicities, infections, neutropenia and thrombocytopenia compared with those patients receiving 5-FU/LV. These data further confirm the favorable safety profile of capecitabine.

Colorectal cancer is more common in older patients so it is important to note that capecitabine was equally well tolerated by older and younger patients. In both subgroups, capecitabine was associated with less diarrhea, nausea, vomiting, stomatitis and neutropenia than 5-FU/LV. Patients aged ≥65 years in the capecitabine arm experienced a similar incidence of early severe toxicities (gastrointestinal toxicities, infections, neutropenia and thrombocytopenia) to the younger patients (aged <65 years), but in the 5-FU/LV arm, patients aged ≥65 years experienced a higher incidence of early severe toxicities compared with patients aged <65 years.

As previously demonstrated in the metastatic setting [18], capecitabine improves medical-resource use compared with 5-FU/LV. Oral capecitabine is administered at home and patients require fewer hospital visits compared with patients receiving i.v. treatment. Administration of 5-FU/LV (Mayo Clinic regimen) requires patients to attend the clinic/hospital for five consecutive days during every 28-day treatment cycle. In addition, the improved safety profile of capecitabine, particularly the significantly lower incidences of diarrhea, nausea/vomiting and neutropenia, leads to a reduced need for medications to manage adverse events.

Good tolerability is a particularly important consideration when chemotherapy is administered in the adjuvant setting. A number of ongoing trials are evaluating 5-FU/LV in combination with irinotecan or oxaliplatin in the adjuvant setting. Recently, results from the MOSAIC study evaluating bolus/infusional 5-FU/LV and oxaliplatin (FOLFOX4) versus infusional 5-FU/LV (the de Gramont regimen) as adjuvant treatment for patients with stage II

or III colon cancer were presented [19]. Although FOLFOX4 achieved a significant improvement in 3-year disease-free survival, this was at the expense of a higher incidence of grade 3 or 4 neutropenia, and 29% of patients experienced long-term (>1 year), low-grade neurotoxicity. Therefore, with FOLFOX4 there is a trade-off between improved outcomes and potential for short- and long-term side effects. In addition, recent preliminary data from the CALGB C89803 trial comparing weekly bolus irinotecan/5-FU/LV with weekly 5-FU/LV (Roswell Park schedule) in the adjuvant setting failed to show any failure-free ($P = 0.88$) or overall survival ($P = 0.92$) benefit associated with the combination arm (letter from principal investigator to National Cancer Institute Cooperative Group Investigators, 26 August 2003). Thus, further studies are needed to establish the benefit of combination chemotherapy over fluoropyrimidine monotherapy.

The improved safety profile of capecitabine versus 5-FU/LV observed in the current trial suggests that capecitabine is an attractive agent to replace 5-FU/LV as the backbone of adjuvant combination treatment for further studies. A large international study has shown that capecitabine in combination with oxaliplatin (XELOX) is a highly active, first-line treatment for metastatic colorectal cancer [20], achieving efficacy similar to that reported for FOLFOX4 with a substantially lower incidence of neutropenia (7% with XELOX versus 42–47% with FOLFOX4 [21, 22]). XELOX is currently being evaluated versus bolus 5-FU/LV (Mayo Clinic or Roswell Park regimen) as adjuvant treatment for chemotherapy-naïve patients with Dukes' C colon cancer. Recruitment of 1850 patients for this trial has begun.

In summary, this analysis shows that from a safety perspective, capecitabine can replace 5-FU/LV as the standard adjuvant treatment for patients with colon cancer. The efficacy results from this study are expected in 2004.

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