Oral Capecitabine Compared With Intravenous Fluorouracil Plus Leucovorin in Patients With Metastatic Colorectal Cancer: Results of a Large Phase III Study

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Purpose: To compare the efficacy and safety of orally administered capecitabine (Xeloda; Roche Laboratories, Inc, Nutley, NJ), a novel fluoropyrimidine carbamate designed to mimic continuous fluorouracil (5-FU) infusion but with preferential activation at the tumor site, with that of intravenous (IV) 5-FU plus leucovorin (5-FU/LV) as first-line treatment for metastatic colorectal cancer.

Patients and Methods: We prospectively randomized 602 patients to treatment with capecitabine 1,250 mg/m² administered twice daily days 1 to 14 every 3 weeks, or to the 4-weekly Mayo Clinic regimen (5-FU/LV) until disease progression or unacceptable toxicity.

Results: The primary objective, to demonstrate at least equivalent response rates in the two treatment groups, was met. The overall response rate was 18.9% for capecitabine and 15.0% for 5-FU/LV. In the capecitabine and 5-FU/LV groups, respectively, median time to disease progression was 5.2 and 4.7 months (log-rank P = .65); median time to treatment failure was 4.2 and 4.0 months (log-rank P = .89); and median overall survival was 13.2 and 12.1 months (log-rank P = .33). The toxicity profiles of both treatments were typical of fluoropyrimidines. However, capecitabine led to significantly lower incidences (P < .00001) of stomatitis and alopecia, but a higher incidence of cutaneous hand-foot syndrome (P < .00001). Capecitabine also resulted in lower incidences (P < .00001) of grade 3/4 stomatitis and neutropenia, leading to a lower incidence of grade 3/4 neutropenic fever and sepsis. Only grade 3 hand-foot syndrome (P < .00001) and uncomplicated grade 3/4 hyperbilirubinemia (P < .0001) were reported more frequently with capecitabine.

Conclusion: Oral capecitabine achieved at least equivalent efficacy compared with IV 5-FU/LV. Capecitabine demonstrated clinically meaningful safety advantages and the convenience of an oral agent.


Colorectal cancer is the third most commonly diagnosed malignancy and the second leading cause of cancer mortality in Europe and the United States that accounts for an estimated 10% to 15% of newly diagnosed cancer cases and approximately 200,000 deaths each year.1,2 Early-stage colorectal cancer is localized and resectable, with a 5-year survival rate of 70% to 80%.3 However, the disease is often asymptomatic in early stages, and up to 30% of patients present with metastatic disease, which has a 5-year survival rate of 5% or less.4 Overall, approximately 50% to 60% of patients eventually develop metastatic or advanced disease.

The fluoropyrimidine fluorouracil (5-FU) is included in treatment regimens for advanced or metastatic colorectal cancer5-10 and results in an increase in survival of approximately 6 months.5,7 Attempts to improve the antitumor efficacy of 5-FU have included biomodulation with agents such as leucovorin, interferon, and L-aspartate and schedule modification using protracted or continuous infusion 5-FU regimens. Both of these approaches have led to superior response rates, but survival benefits have been modest (< 1.5 months) at best,11,12 with several studies and meta-analyses failing to identify any clinically significant survival advantage.13-17 Orally administered fluoropyrimidine derivatives have been designed as an alternative approach to optimizing

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5-FU–based therapy and have been shown to deliver 5-FU to target cells with predictable kinetics.\textsuperscript{18,19} Oral administration achieves sustained cytotoxic exposure and enables fine control of dosing. In addition, oral agents are more convenient to administer than intravenous (IV) 5-FU, and most patients prefer oral chemotherapy to IV regimens.\textsuperscript{20-22}

Capecitabine, an oral fluoropyrimidine carbamate, was rationally designed with the aim of delivering 5-FU predominantly to the tumor cells.\textsuperscript{23-25} Capecitabine is rapidly and extensively absorbed as an intact molecule and is then metabolized to 5-FU in three steps. First, it is converted to 5'-deoxy-5-fluorocytidine by hepatic carboxylesterase (primarily in the liver), then to 5'-deoxy-5-fluorouridine by cytidine deaminase (in tumor cells and liver), and finally to 5-FU by thymidine phosphorylase, which is significantly more active in tumor tissue than in adjacent healthy tissue.\textsuperscript{24,26} Because each step of metabolic conversion occurs with successively greater specificity for tumor cells, capecitabine potentially reduces systemic exposure to 5-FU while maximizing the dose-intensity of 5-FU within tumor tissue. Preferential tumor activation of capecitabine has been demonstrated in patients with colorectal cancer.\textsuperscript{27}

In a randomized phase II study, an intermittent regimen of capecitabine (twice daily at 1,250 mg/m\textsuperscript{2} for 14 days followed by a 7-day rest period) for at least 12 weeks led to tumor responses in eight (24\%) of 34 patients and median time to tumor progression (TTP) of 7.7 months.\textsuperscript{28} This regimen was generally well-tolerated and allowed administration of a higher dose-intensity than was possible with either continuous twice-daily capecitabine monotherapy or intermittent capecitabine in combination with leucovorin. In view of these promising results, we performed one of two large, prospective, randomized, phase III trials\textsuperscript{29,30} with identical protocols, conduct, and monitoring to determine whether the intermittent regimen of oral capecitabine defined in the phase II study was at least as active as standard treatment with the Mayo Clinic regimen, 5-FU plus leucovorin (5-FU/LV). This article presents the final results of one of the trials.

**PATIENTS AND METHODS**

**Patients**

Patients were eligible for this study if they had advanced or metastatic colorectal cancer and had not received prior chemotherapy for metastatic disease. Adjuvant chemotherapy, if administered, must have been completed at least 6 months before enrollment onto the trial. Histologic or cytologic confirmation of colorectal adenocarcinoma was required, as well as the presence of at least one bidimensionally measurable indicator lesion that had not been irradiated. Ascites and pleural effusion were not considered measurable. One or more indicator lesions were required to be at least 10 mm in one dimension in the lung or skin or at least 20 mm in one dimension in the liver or soft tissue masses. Patients had to be at least 18 years of age, ambulatory (Karnofsky performance status $\geq 70\%$), have a life expectancy of at least 3 months, and must have given written informed consent. Contraception was required throughout treatment for females of childbearing potential and for sexually active males. Patients were not included if they were pregnant or lactating, if they were hypersensitive to 5-FU or had previously experienced a severe reaction to fluoropyrimidines, if they had received other experimental drugs within 4 weeks before enrollment, if they had a history of other cancer within the previous 5 years (except for cured basal cell carcinoma of the skin or cervical cancer-in-situ), if they had received radiotherapy for their disease within the previous 4 weeks, or had not fully recovered from recent (within 4 weeks) major surgery. Also excluded were patients with organ allografts, CNS involvement of their disease, neurologic or psychiatric disorders that could interfere with treatment compliance, significant cardiac disease or a myocardial infarction within the previous 12 months, serious uncontrolled infections, malabsorption syndrome, or if they lacked physical integrity of their upper gastrointestinal tract. Patients were also not enrolled if screening evaluations revealed significant abnormalities in neutrophils ($< 1.5 \times 10^9$/L), platelets ($< 100 \times 10^9$/L); serum creatinine or serum bilirubin ($> 1.5 \times$ upper normal limit); ALT; AST; or alkaline phosphatase ($> 2.5 \times$ upper normal limit). However, up to five times the upper normal limit for ALT, AST, and alkaline phosphatase was allowed in patients with liver metastases, and up to 10 times upper normal limit for alkaline phosphatase was allowed in patients with bone disease. The study was conducted in accordance with the Declaration of Helsinki and all current amendments, and the study protocol was approved by institutional review boards at each participating clinical institution.

**Study Design and Treatment**

This was an open-label, randomized, parallel-group study conducted at 59 centers in Europe, Australia, New Zealand, Taiwan, and Israel. After screening to establish eligibility, patients were randomized to treatment with capecitabine or 5-FU/LV through a computer-assisted touch-tone randomization center. The patients were randomized centrally by country, in blocks of six patients, but with Australia, New Zealand, and Taiwan grouped as a single location. There was no further stratification.

**Treatment Schedules**

Capecitabine was administered orally twice daily at 1,250 mg/m\textsuperscript{2} (equivalent to a total dose of 2,500 mg/m\textsuperscript{2}/d) as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by 1 week’s rest). For practical reasons, capecitabine doses were rounded to the nearest dose that could be administered with a combination of 500 mg and 150 mg tablets. Capecitabine was given at approximately 12-hour intervals and was taken orally with water within 30 minutes of a meal (breakfast or dinner). The 5-FU/LV was administered according to the Mayo Clinic regimen, which consists of LV 20 mg/m\textsuperscript{2} as a rapid IV injection followed by an IV bolus injection of 5-FU 425 mg/m\textsuperscript{2}, administered daily for 5 days in 4-week cycles. Treatment with capecitabine or 5-FU/LV was continued until the scheduled assessment at 30 weeks or until the development of progressive disease if recorded earlier. In responding patients and those with stable disease, treatment could be continued for up to 48 weeks or for longer at the discretion of the investigator.

**Treatment Modifications**

Treatment interruption or dose reduction was not indicated for reactions unlikely to become serious or life-threatening, or for grade 1 toxicity (National Cancer Institute of Canada Common Toxicity Criteria [NCIC CTC]). No dose reduction was required for the first
appearance of a grade 2 toxicity. Treatment with capecitabine was interrupted in cases of grade 2 toxicity or worse and was not resumed until toxicity resolved or improved to grade 1. When treatment was resumed, capecitabine doses were reduced as follows: (1) by 25% for patients who experienced a second occurrence of a given grade 2 toxicity or any occurrence of grade 3 toxicity or (2) by 50% for patients who experienced a third occurrence of a given grade 2 toxicity, a second occurrence of a given grade 3 toxicity, or any occurrence of grade 4 toxicity. Treatment was discontinued if a given toxicity occurred, despite dose reduction, for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4.

For patients allocated to treatment with 5-FU/LV, the dose of LV was held constant, and 5-FU doses were escalated or reduced according to toxicity. If initial treatment led to no toxicity, the 5-FU dose could be escalated by 10% for the next cycle. No change in 5-FU dose was indicated for patients who experienced grade 1 toxicity. The 5-FU dose was decreased as follows: by 20% in cases of grade 3 hematologic toxicity, or grade 2 nonhematologic toxicity and by 30% in cases of grade 4 hematologic toxicity or for grade 3 or 4 nonhematologic toxicity. Treatment was discontinued if a patient experienced both hematologic and nonhematologic grade 4 toxicity.

**Evaluation of Patients**

Assessments of tumor dimensions and involved sites were performed before the start of treatment and were scheduled during therapy after weeks 6, 12, 18, 24, and 30. Further assessments were performed after weeks 39 and 48 for patients who received prolonged therapy (48 weeks). Follow-up assessments for disease progression and survival monitoring were performed every 3 months after the end of treatment. Tumor dimensions were assessed using computed tomography scans, x-rays, or magnetic resonance imaging, with tumor response classification based on standard World Health Organization criteria. Complete response (CR) required the disappearance of all known disease at all involved sites. Partial response (PR) was defined as residual disease with a decrease $\geq 50\%$ in the sum of the products of greatest perpendicular diameters (SPD) of indicator lesions. Progressive disease (PD) was defined as the appearance of a new lesion, or an increase of 25% in SPD. Stable disease was defined as no change in SPD or a change not corresponding to CR, PR, or PD. To ensure consistency in evaluation, successive tumor measurements and response evaluations for a given patient were conducted by the same investigator. All indicator lesions for evaluation of tumor response were bidimensionally measurable and had not been treated with radiotherapy. Investigator assessments of tumor response were reviewed by an independent review committee (IRC) composed of radiologists. Members of the IRC were blinded to the treatment received, clinical condition of the patient, and to the investigator’s evaluation and measurements. The IRC-assessed tumor response solely on the basis of x-ray or other imaging. Oncologists were available for IRC consultation.

Safety evaluations were conducted at least monthly until 4 weeks after the last administration of therapy, and included assessments of clinical adverse reactions and laboratory parameters. Adverse events were graded on a four-point scale as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4), as classified by the NCIC CTC grading system (revised December 1994). Hand-foot syndrome (palmar-plantar erythrodysesthesia) was classified as grade 1 (numbness, dysesthesia, painless swelling, or erythema not disrupting normal activities), grade 2 (painful erythema with swelling or affecting daily living activities), or grade 3 (moist desquamation, ulceration, blistering, severe pain, or any symptoms leading to an inability to work or to perform daily living activities).

**Statistical Analysis**

The primary end point for this study was the overall objective tumor response rate (CR and PR). The study was designed principally to determine whether capecitabine was at least as active as 5-FU/LV in the induction of tumor responses. A sample size of 302 patients per treatment group in the all-randomized population was sufficient to achieve 80% power to demonstrate at least equivalence in overall response rates, assuming a 20% response rate in both the capecitabine and 5-FU/LV treatment groups, a margin of equivalence of 10%, with alpha equal to 0.025. The at least equivalence test was based on confidence intervals for the difference in response rates according to Hauck-Anderson. In case the at least equivalence test was passed, a further test (two-sided at alpha = 0.05) on differences in response rates was performed using a $\chi^2$ test with Schouten correction. The study was also powered (80%) for a difference of 20% versus 30% in overall response rate between the two treatment groups.

Secondary efficacy end points were time to response, duration of response, TTP, time to treatment failure, overall survival and quality of life (results to be published separately). Duration of response was calculated according to the World Health Organization response criteria. TTP was calculated from the date of randomization to the first recorded observation of PD or death from any cause. Time to treatment failure included, in addition, premature withdrawals because of adverse events, patients who failed to return, and treatment refusals as events. Overall survival was calculated from the date of randomization to the date of death from any cause. Results for TTP and overall survival were analyzed according to Kaplan-Meier estimates and compared using the log-rank test. In addition, Cox proportional hazards models were applied to test for interactions between prognostic factors and overall survival. Laboratory parameters (hemoglobin and alkaline phosphatase) were analyzed as continuous parameters in the model.

All analyses of efficacy are reported for the all-randomized population, and all analyses of safety are based on the safety population, which included all patients who received at least one dose of study drug. The IRC assessment was not designed to provide a complete clinical assessment of time-related end points such as TTP and time to treatment failure. These parameters were analyzed using the investigator assessments, and therefore, for reasons of consistency, the response rate data were also analyzed and reported according to the investigator assessments as well as the IRC assessments.

Adverse reactions, laboratory abnormalities, hospitalizations, and treatment administered for adverse reactions were summarized as incidence rates. For clinically relevant, predefined grade 3/4 adverse reactions typically associated with fluoropyrimidines (diarrhea, stomatitis, hand-foot syndrome, alopecia, nausea, vomiting, and neutropenia) a Kaplan-Meier estimate for the time from randomization to first onset of these adverse reactions was calculated. The log-rank test was used to test for treatment differences.

**RESULTS**

**Patients and Treatment**

A total of 602 patients were randomized to treatment with capecitabine (301 patients) or 5-FU/LV (301 patients). Patients were enrolled from 59 centers during a 16-month period from October 2, 1996, to February 4, 1998. Table 1 lists demographic data, baseline disease characteristics, and prior treatment for colorectal cancer for all randomized...
Overall, the two treatment groups were well-balanced for all evaluated characteristics. Most patients were elderly, and the colon was the more common site of primary tumor. In both treatment groups, 16% to 17% of patients had tumors with poorly differentiated histology. All patients had advanced or metastatic disease, and the most frequently involved metastatic sites were liver (78%), lung (30%), and lymph nodes (28%).

Of the 602 patients enrolled, 596 patients received at least one dose of the allocated treatment drug, approximately 80% completed 6 weeks of therapy, and approximately 28% completed the planned treatment period of 30 to 32 weeks. The most frequent reasons for treatment discontinuation were progressive disease (153 patients in the capecitabine group and 165 in the 5-FU/LV group), adverse reactions (40 patients in the capecitabine group and 32 in the 5-FU/LV group), and treatment refusals (20 patients in each group).

Both treatment groups adhered well to the planned dosage regimens. For patients treated with capecitabine, the median dose per cycle was between 82% and 100% of that planned. The lower end of median dose per cycle was the result of protocol-specified treatment interruption for toxicity. The median duration of capecitabine treatment was 147 days. For patients treated with 5-FU/LV, the median dose per cycle of 5-FU was between 95% and 100% of that planned. The median duration of treatment was 140 days. For both treatment groups, therefore, actual treatment deviated from planned treatment to only a minor extent and to a similar degree.

Primary Efficacy End Point: Overall Response Rate

The overall response rates, according to the IRC assessment, were statistically at least equivalent for capecitabine compared with 5-FU/LV, thus meeting the primary objective of the study. The response rate was 18.9% (95% confidence interval [CI], 14.7% to 23.8%) with capecitabine, compared with 15.0% (95% CI, 11.1% to 19.5%) with 5-FU/LV (Table 2). The investigator-assessed response rate in patients treated with capecitabine was 26.6% (95% CI, 21.7% to 32.0%), compared with 17.9% (95% CI, 13.8% to 22.8%) in the 5-FU/LV group ($P = .013$).

Secondary Efficacy End Points

As an indicator of time to response, the numbers of patients who responded were grouped into 6-week treatment intervals. In both treatment groups, responses usually occurred within the first 12 weeks of therapy. However, throughout all time periods, more patients responded to capecitabine treatment than to 5-FU/LV.

The median duration of response in responding patients (PR or CR) was 7.2 months in the capecitabine group and 9.4 months in the 5-FU/LV group ($P = .17$). Median TTP, which was at least equivalent to capecitabine compared with 5-FU/LV, was 5.2 months and 4.7 months, respectively (Fig 1). No difference was apparent between the treatment groups (log-rank $P = .65$; hazards ratio, 0.96 [95% CI, 0.81 to 1.14]). Time to treatment failure was similar in both treatment groups, with a median of 4.2 months in the capecitabine treatment arm and 4.0 months in the 5-FU/LV arm (log-rank $P = .89$). Survival for patients in the
The capecitabine group was equivalent to the 5-FU/LV group (hazards ratio, 0.92 [95% CI, 0.78 to 1.09]; log-rank \( P = .33 \)), with a median survival of 13.2 months for capecitabine and 12.1 months for 5-FU/LV (Fig 2).

A multivariate Cox regression analysis identified elevated alkaline phosphatase at baseline, poor Karnofsky performance status (70% or 80% vs 100%), multiple versus single sites of metastasis, and liver as the predominant site of metastases as significant prognostic factors correlated with reduced overall survival in both treatment groups independent of assigned treatment for all prognostic factors.

**Toxicity Profile**

The toxicity profile of capecitabine is typical of infused fluoropyrimidines, and clinically important safety advantages over the Mayo Clinic regimen were observed. Patients in the capecitabine group experienced significantly less stomatitis and alopecia of any grade compared with the 5-FU/LV group \( (P < .00001) \), whereas hand-foot syndrome, a cutaneous syndrome affecting palms and soles, was more frequent in patients treated with capecitabine \( (\chi^2 \ P < .00001) \). Figure 3 depicts the frequency of treatment-related adverse reactions reported at any grade for more than 15% of patients in at least one of the treatment groups.

Table 3 lists the incidence of all grade 3 adverse reactions reported for more than 5% of patients in at least one of the treatment groups and all grade 3 or 4 adverse reactions reported in at least 1% of the patients with at least one grade 4 adverse event. Treatment with 5-FU/LV led to a higher incidence of grade 3 or 4 stomatitis \( (P < .00001) \) and of neutropenic fever or sepsis, whereas capecitabine led to a higher incidence of grade 3 hand-foot syndrome \( (P < .00001) \). Overall, few patients experienced grade 4 toxicity in either group. Grade 4 reactions that occurred in only one patient (and, therefore, not reported in Table 3) were myocardial infarction, rectal bleeding, pulmonary embolism, cholestatic hepatitis, drug hypersensitivity in the capecitabine group and hypotension, impaired diabetic control, cardiac failure not otherwise specified, respiratory distress, renal failure not otherwise specified, and hyperosmolarity in the 5-FU/LV group.

Severe cardiotoxicity and neurotoxicity were infrequent in both treatment groups. Treatment-related grade 3 or 4 cardiac toxicity was reported for two patients (0.7%) in the capecitabine group (one case each of myocardial infarction and tachycardia) and three patients (1.0%) in the 5-FU/LV group (one case each of cardiac failure, myocardial infarction, and edema). Treatment-related grade 3 or 4 neurotoxicity was reported for two patients (0.7%) in the capecitabine group (one case each of taste disturbance and syncope) and one patient (0.3%) in the 5-FU/LV group (dizziness).

Diarrhea, stomatitis, nausea, vomiting, alopecia, hand-foot syndrome, and neutropenia are known to be the most frequent adverse events associated with fluoropyrimidines and are events that have a serious impact on quality of life.
or constitute dose-limiting toxicities that require dose modifications. A protocol-prespecified safety analysis, therefore, focused on the time to onset and the incidence of treatment-related grade 3 and 4 episodes of these events. It demonstrated a statistically significant difference that favored capecitabine, indicating a later onset and a lower incidence of these grade 3 or 4 adverse reactions (log-rank $P = .008$) (Fig 4).

Adverse reactions led to fewer hospitalizations in the capecitabine group than in the 5-FU/LV group ($35 \div 47$ patients) (Table 4). Hospitalization for diarrhea occurred with similar frequency in both treatment groups, whereas hospitalization for stomatitis was required more often for patients treated with 5-FU/LV. Two patients in the capecitabine group were hospitalized because of hand-foot syndrome. Patients in the capecitabine group were also less likely to require symptomatic treatment for certain adverse reactions than patients in the 5-FU/LV group (Table 5), notably for stomatitis ($38\% \div 72\%$ of affected patients, respectively), and diarrhea ($57\% \div 68\%$ of affected patients, respectively), with more patients in the capecitabine group requiring treatment for hand-foot syndrome ($54\% \div 19\%$).

Table 6 shows the incidence of grade 3 or 4 abnormalities in laboratory parameters. Myelosuppression was rarely seen with capecitabine, whereas the incidence of grade 3 and 4 neutropenia or granulocytopenia was $19.7\%$ with 5-FU/LV. Increases in transaminases or alkaline phosphatase levels were rarely observed in either group. Using the NCIC CTC criteria, reversible grade 4 hyperbilirubinemia was seen in $4.7\%$ in the capecitabine arm and in $3.3\%$ in the 5-FU/LV arm. More grade 3 hyperbilirubinemia was observed with capecitabine than with 5-FU/LV ($23.6\% \div 3.0\%; P < .0001$). Notably, grades 3 and 4 hyperbilirubinemia correspond to grades 2 and 3 in the revised, updated NCI CTC criteria (version 2.2, July 21, 1999).

Of the 84 patients with elevated bilirubin in the capecitabine group, 8 ($10\%$) had concomitant grade 3 abnormalities in ALT or AST. By comparison, of the 19 patients with elevated bilirubin in the 5-FU/LV group, nine patients ($47\%$) had concomitant grade 3 or 4 abnormalities in either bilirubin plus alkaline phosphatase or liver transaminases. No cumulative increases in bilirubin were seen.

### Table 3. Grade 3 and Grade 4 Adverse Reactions Related to Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Capecitabine (n = 297)</th>
<th>5-FU/LV (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>9.4</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>48</td>
<td>16.2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable.

*An adverse reaction is listed if reported at grade 3 in $>5\%$ of patients in at least one of the treatment groups and all adverse grade 3 or 4 reactions reported in $\geq 1\%$ of the patients with at least one grade 4 adverse event.

### Table 4. Hospitalization Required for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Capecitabine (n = 297)</th>
<th>5-FU/LV (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>All adverse reactions</td>
<td>35</td>
<td>11.8</td>
</tr>
<tr>
<td>Dehydration</td>
<td>5</td>
<td>1.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>4.4</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Fig 4. Time to first onset of prespecified treatment-related grade 3 and 4 adverse reactions.
Adverse reactions led to dose reductions in 27.3% of patients in the capecitabine group (most commonly for hand-foot syndrome and diarrhea) and in 35.1% of patients in the 5-FU/LV group (most commonly for stomatitis and diarrhea). Dose reductions for adverse reactions were required earlier in the 5-FU/LV group (median, 36 days) than in the capecitabine group (median, 91 days). Treatment was discontinued because of adverse reactions in 10.1% of patients in the capecitabine group and in 7.0% of patients treated with 5-FU/LV. The most frequent adverse reactions leading to discontinuation either alone or in combination were diarrhea (2.0%), hand-foot syndrome (1.7%), and nausea (1.0%) in the capecitabine group and diarrhea (2.0%) and stomatitis (1.7%) in patients treated with 5-FU/LV. Treatment-related adverse reactions were fatal for three patients in the capecitabine group (one case each of gastrointestinal necrosis, pulmonary embolism, and myocardial infarction), and for four patients treated with 5-FU/LV (one case each of cardiac failure, renal tubular necrosis, sepsis, and enterocolitis).

**DISCUSSION**

This randomized, phase III study was designed to compare the efficacy and toxicity of oral capecitabine with that of the Mayo Clinic regimen, IV bolus 5-FU/LV, as first-line treatment in patients with advanced or metastatic colorectal cancer. The results of this trial demonstrate that capecitabine has at least equivalent efficacy compared with IV 5-FU/LV. This study also indicates that capecitabine has clinically meaningful safety advantages over 5-FU/LV.

Baseline disease characteristics, demographic features, treatment history, and prognostic factors were similar between the two treatment groups, and are consistent with those in other studies of colorectal cancer patients who receive first-line 5-FU-based chemotherapy. This trial, therefore, provides a sound basis for establishing the activity of capecitabine, and the results seem to be generally applicable to patients with advanced or metastatic colorectal cancer.

Response rates in the all-randomized population based on the IRC assessment were at least equivalent with capecitabine compared with 5-FU/LV (Table 2). The response rates observed in the 5-FU/LV group in this study were consistent with those reported for the same 5-FU/LV regimen in other trials, indicating that the patients included in this study were representative of typical populations that receive first-line therapy for metastatic colorectal cancer.

### Table 5. Treatment Required for Adverse Reactions*

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine (n = 297)</th>
<th>5-FU/LV (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With AE (no.)</td>
<td>65</td>
<td>163</td>
</tr>
<tr>
<td>Patients Treated For AE (no.)</td>
<td>25</td>
<td>117</td>
</tr>
<tr>
<td>Patients Receiving Treatment (%)</td>
<td>38</td>
<td>72</td>
</tr>
<tr>
<td>Patients Receiving Treatment (%)</td>
<td>38</td>
<td>72</td>
</tr>
</tbody>
</table>

**Table 6. Grade 3 or 4 Abnormalities in Laboratory Parameters**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>Capcitabine (n = 297)</td>
<td>5-FU/LV (n = 299)</td>
<td>5-FU/LV (n = 299)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>8</td>
<td>2.7</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Leukocytes, WBC</td>
<td>5</td>
<td>1.7</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Neutrophils*</td>
<td>0</td>
<td>0.7</td>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>Platelets</td>
<td>2</td>
<td>0.3</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>70</td>
<td>23.6</td>
<td>14</td>
<td>4.7</td>
</tr>
<tr>
<td>ALT</td>
<td>2</td>
<td>0.7</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>AST</td>
<td>2</td>
<td>0.7</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>8</td>
<td>2.7</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>11</td>
<td>3.7</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Includes reports of neutropenia or granulocytopenia.
The toxicity of capecitabine differed in important respects from that of 5-FU/LV. Capecitabine was associated with a substantially lower incidence of the clinically important toxicities, such as severe stomatitis, leucopenia, and neutropenia leading to less neutropenic fever and sepsis compared with 5-FU/LV. Although capecitabine and 5-FU/LV both induced toxicities characteristic of fluoropyrimidines, the onset of typical grade 3 and 4 fluoropyrimidine-related adverse reactions was significantly later and less frequent with capecitabine (Fig 4). Consequently, dose reductions occurred later in patients treated with capecitabine than in those receiving 5-FU/LV. Thus, 27.3% of the capecitabine patients and 35.1% of the 5-FU/LV patients required dose reduction, and median time to dose reduction was 91 days with capecitabine versus 36 days with 5-FU/LV. The results of this analysis are clinically relevant because patients who develop progressive disease during the early treatment period will have experienced less drug-related toxicity before discontinuing treatment. Moreover, adverse reactions leading to hospitalization were less frequent in the capecitabine group.

Patients treated with capecitabine who developed hand-foot syndrome responded to dose interruption or reduction according to the protocol and to topical emollients, with improvement and resolution of symptoms. Although 48% of patients developed some degree of hand-foot syndrome at the planned dose-intensity of capecitabine, only approximately half of those required treatment, which consisted mainly of topical emollients. Only two patients were hospitalized, both for less than 24 hours (one patient had an inpatient visit without overnight stay, and the other had one overnight stay for observation only), and fewer than 2% withdrew from treatment because of this cutaneous reaction. This indicates that hand-foot syndrome did not present a major problem for patients and investigators. In addition, most patients who developed hand-foot syndrome subsequently tolerated treatment with a reduced dose of capecitabine.

Patients in the capecitabine group experienced a higher incidence of NCIC CTC grade 3 or 4 hyperbilirubinemia. However, this hyperbilirubinemia was not clinically significant. Indeed, this level of hyperbilirubinemia corresponds to only grade 2 or 3 bilirubin in the updated and revised NCI CTC criteria. Elevated bilirubin was generally not accompanied by concomitant abnormalities in liver transaminases or alkaline phosphatase, and none of the cases of elevated bilirubin were reported to be irreversible.

The results of this trial were supported by data from an identical trial conducted in the United States, Canada, Mexico, and Brazil, which included 605 patients receiving first-line therapy for metastatic colorectal cancer. Capecitabine therapy in this trial resulted in a significantly superior response rate in patients receiving capecitabine (investigator assessment: 24.8% vs 15.5% with 5-FU/LV; \( P = .005 \); IRC assessment: 25.8% vs 11.6% with 5-FU/LV; \( P = .001 \)), and TTP and survival were equivalent for capecitabine and 5-FU/LV.

In addition, the results of the American trial and the present European trial have been combined, and a prospective analysis of the integrated data has been conducted. The integrated analysis confirmed the results of the individual trials in terms of both efficacy and safety. Capecitabine demonstrated a significantly superior response rate (investigator assessment: 25.5% vs 16.7% with 5-FU/LV, \( P < .00002 \); IRC assessment: 22.4% vs 13.2% with 5-FU/LV, \( P < .0001 \)) and equivalent TTP and survival. The toxicity profile of capecitabine was similar to that observed in the present study, with a significantly lower incidence of key adverse events (diarrhea, stomatitis, nausea, and alopecia). Hand-foot syndrome was significantly more common with capecitabine but rarely led to treatment withdrawal and resulted in only two brief hospitalizations.

Regimens of 5-FU/LV have been considered standard therapy for patients with advanced colorectal cancer for many years. The Mayo Clinic regimen is widely used because of its convenience and its greater activity in the induction of response rates compared with bolus 5-FU alone. Response rates reported with the Mayo Clinic regimen range from 9% to 43%, with median survival typically ranging from 10 to 13 months and similar to those observed with other 5-FU/LV regimens. Administering 5-FU as a prolonged continuous infusion leads to significant increases in response rates compared with bolus 5-FU alone, but this has resulted in only a minimal survival benefit or no survival at all. Several studies have demonstrated that an infused regimen of 5-FU/LV (de Gramont or German Association of Medical Oncology regimen) induces a higher response rate compared with IV bolus 5-FU/LV (Mayo Clinic regimen), but no survival difference was observed.

Disadvantages of infused 5-FU include inconvenience because of technical requirements, such as central venous access, portable pumps and cost, and the 15% to 20% incidence of significant complications, including infections, bleeding, thrombosis, and pneumothorax, which have a negative impact on quality of life. In a randomized European Organization for Research and Treatment of Cancer trial in which patients received either an oral fluoropyrimidine or the Mayo Clinic regimen as first-line therapy for colorectal cancer and after the first cycle were crossed over to the alternative treatment, 84% of the patients expressed a preference for the oral treatment. The main reasons provided for this preference were oral therapy, decreased incidence of mouth sores, home-
based therapy (69%), and decreased interruption of daily activities (46%).

Since the start of the present study, other therapeutic agents have demonstrated activity in advanced colorectal cancer either as monotherapy or in combination with 5-FU. Promising results have been obtained with irinotecan in patients with advanced colorectal cancer who have not responded to prior 5-FU therapy35,46 and as first-line therapy in combination with 5-FU/LV.42,43 The combination of capecitabine plus irinotecan is currently being investigated in several clinical trials.47-49 Similarly, the combination of capecitabine plus oxaliplatin is being explored50,51 on the basis of reports that oxaliplatin and 5-FU/LV may have synergistic activity in patients with advanced colorectal cancer.52 The combination of capecitabine and radiotherapy for rectal cancer is being studied in several phase II/III trials, particularly in the neoadjuvant setting, to replace more cumbersome protracted 5-FU infusions parallel to radiotherapy.53 Phase I trials of the triple combination irinotecan, oxaliplatin, and capecitabine are in the planning phase, and clinical trials of an all-oral combination of capecitabine plus oral irinotecan are being conducted. On the basis of the results of the present study, we conclude that capecitabine monotherapy provides advantages compared with IV bolus 5-FU/LV in the treatment of advanced colorectal cancer, including a favorable toxicity profile and the convenience of an oral drug that is more attractive to patients, enabling convenient outpatient therapy.

APPENDIX

In addition to the members of the writing committee, the following investigators of the Xeloda Colorectal Cancer Study Group took part in this trial: K. Pittman, MD, and D. Wyld, MD, Brisbane; D. Dalley, MD, Sydney; M. Green, MD, Melbourne, Australia; D. Schrijvers, MD, Antwerp, Belgium; H. Naman, MD, Cannes; H. Cure, MD, Clermont Ferrand; B. Audhuy, MD, Colmar; P. Solal-Celigny, MD, Le Mans; F.X. Caroli-Bosc, MD, Nice; E.M. Marty, Paris; P. Dufour, Strasbourg, France; T. Sauerbruch, MD, Bonn; H.E. Blum, Freiburg; W.E. Fleig, Halle; J. Mössner, MD, Leipzig; R. Porsch, Tübingen; M.P. Lutz, MD, Ulm, Germany; A. Figler, MD, Petah Tikva; A. Shani, Rehovot, Israel; A. Cassata, MD, Milano; E. Pasquini, MD, Cattolica; A. Sobrero, and A. Gozza, Genoa; A. Goldhirsch, and E. Villa, Milan; P.F. Conte, MD, Pisa; C. Sternberg, MD, Rome, Italy; A. Garin, K.N. Salamov, and Y.A. Shelygin, Moscow; V. Moiseyenko, St Petersburg, Russia; M. Navarro Garcia, MD, Barcelona; P. Costas Rojo, MD, Getafe, Spain; T.Y. Chao, MD, K.H. Yeh, MD, and C.H.J. Yang, MD, Taipei, Taiwan; S. Falk, MD, Bristol; D. Jodrell, MD, Edinburgh; N. Bailey, MD, Gateshead; D. Dunlop, MD, and M. Soukop, MD, Glasgow; P. Selby, Leeds; W. Stewart, Leicester; R. Glyane-Jones, MD, Northwood; F. Daniel, MD, Plymouth; J. Primrose, Southampton; D. Cunningham, MD, Sutton, United Kingdom; and A. Tibault, MD, Nutley, NJ.

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