Randomized Multicenter Phase II Trial of Two Different Schedules of Irinotecan Combined with Capecitabine as First-Line Treatment in Metastatic Colorectal Carcinoma

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BACKGROUND. The aim of the current randomized Phase II study was to investigate the efficacy and safety of capecitabine combined with irinotecan as first-line treatment in metastatic colorectal carcinoma (CRC).

METHODS. A total of 140 patients received capecitabine at a dose of 1250 mg/m^2 twice daily on Days 2–15 and irinotecan at a dose of either 300 mg/m^2 on Day 1 (Arm A) or 150 mg/m^2 on Days 1 and 8 (Arm B) every 3 weeks. During the course of the study, enrollment was continued using lower doses of capecitabine (1000 mg/m^2 twice daily) and irinotecan (Arm A: 240 mg/m^2; Arm B: 120 mg/m^2) to improve the safety profile of the combinations.

RESULTS. Efficacy was evaluable in 134 patients (68 in Arm A, 66 in Arm B). Objective responses were observed in 46% of the patients (8% complete response [CR]), including 47% in Arm A (9% CR; 38% partial response [PR]) and 44% in Arm B (8% CR; 36% PR). The median progression-free survival was 8.3 months in Arm A and 7.6 months in Arm B. Among the first 52 patients treated with the higher doses, the most frequent Grade 3–4 adverse event was diarrhea (27%). The lower doses adopted in the subsequent 88 patients led to better diarrhea control, particularly in Arm A, and significant reductions in the incidence of all-grade hand-foot syndrome and abdominal pain.

CONCLUSIONS. The capecitabine and irinotecan combination was a highly active first-line therapy in metastatic CRC. An acceptable safety profile was observed after dose reduction, particularly when irinotecan was administered on 1 day. ***Cancer* 2004;100:279–87.** © *2003 American Cancer Society.*

KEYWORDS: colorectal carcinoma, first-line treatment, irinotecan and capecitabine combination, Phase II trial.

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Colorectal carcinoma (CRC) is the third most frequent cancer worldwide. Approximately 780,000 new cases are diagnosed every year throughout the world and the estimated annual death rate is 440,000.[1] Early-stage CRC is localized and resectable, but 20% of the patients have metastatic disease at the time of diagnosis and 50% of all patients eventually die of the disease. Furthermore, the 5-year overall survival rate for patients with metastatic CRC is $< 10\%$.[2]

Until recently, the therapeutic options for advanced CRC were mainly confined to chemotherapy with 5-fluorouracil (5-FU), which is included in almost all standard and experimental regimens for advanced or metastatic disease.[3,4] Attempts to improve the antitumoral efficacy of 5-FU have included continuous infusion regimens and biomodulation with leucovorin (LV).[5–8] However, although both approaches have led to better response rates, the survival benefits have been modest and a number of studies and meta-analyses have failed to find any clinically significant advantage.[9,10]

The recent development of new cytotoxic drugs and alternatives to 5-FU with substantial antitumoral activity in CRC has dramatically changed treatment strategies and therapeutic goals in patients with advanced disease.[11] A particularly promising approach to optimizing 5-FU–based therapy has been the development of oral fluoropyrimidine derivatives designed to mimic continuous 5-FU infusions and deliver the drug to target tumor cells.[12–15] Capecitabine is an oral fluoropyrimidine carbamate that mainly delivers 5-FU to tumor cells. It is rapidly and extensively absorbed as an intact molecule and then metabolized to 5-FU in three steps: 1) conversion to 5′-deoxy-5-fluorocytidine by means of hepatic carboxylesterase (primarily in the liver); 2) conversion to 5′-deoxy-5-fluorouridine by means of cytidine deaminase (in tumor cells and the liver); and 3) conversion to 5-FU by means of thymidine phosphorylase, which is significantly more active in tumor tissue than in adjacent healthy tissue.[16,17] The increasing specificity for tumor cells at each conversion step potentially reduces systemic 5-FU exposure while increasing the 5-FU dose inside tumor tissue.

Two randomized Phase III trials comparing the efficacy and tolerability of capecitabine with those of intravenous (i.v.) bolus 5-FU/LV in the first-line treatment of advanced CRC have shown equivalent efficacy in terms of median time to disease progression and overall survival, although to our knowledge, only one study found a significantly higher response rate for capecitabine.[18,19] Furthermore, a safety analysis revealed that capecitabine offers a clinically meaningful advantage over 5-FU/LV in terms of safety, with fewer National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC) Grade 3–4 adverse reactions occurring in the patients receiving capecitabine than in those treated with bolus 5-FU/LV.[20] However, to the best of our knowledge, no studies published to date have compared capecitabine with continuous 5-FU infusion.

Another important drug approved for the treatment of CRC is irinotecan (CPT-11), a semisynthetic derivative of camptothecin that targets topoisomerase I.[21–23] Irinotecan has led to promising results in patients with advanced CRC who failed to respond to previous 5-FU therapy[24,25] and the available evidence suggests the absence of any cross-resistance between it and 5-FU. Two large randomized trials have demonstrated that, compared with 5-FU/LV alone, the addition of irinotecan to bolus or infusional 5-FU significantly improves response rates, median time to disease progression, and overall survival in previously untreated patients.[26,27] The originally reported incidence of treatment-related deaths possibly associated with the administration of weekly irinotecan plus bolus 5-FU/LV initially led to the suggestion that irinotecan plus continuous 5-FU infusion may be a safer regimen, but the two regimens have never been compared in a prospective study.[28]

In addition to offering improved efficacy and tolerability in comparison to 5-FU/LV, capecitabine is more convenient to administer than i.v. 5-FU, a factor that is particularly important to patients receiving therapy for late-stage disease, who tend to prefer oral chemotherapy.[29,30] Capecitabine and irinotecan have different mechanisms of action and show only a partial overlap of key toxicities.[31,32] Preclinical studies of 5-FU and irinotecan combination therapy showed additive activity.[33] The sequential combination of low-dose irinotecan (Day 1) followed by capecitabine (Days 2–15) has been found to be highly curative and selective against both in vitro and in vivo tumor models.[34] The therapeutic index and maximum tolerated dose of irinotecan and capecitabine regimens have been investigated in patients with metastatic CRC.[35–37] Given the promising results, we performed this randomized Phase II trial to evaluate the antitumor activity and tolerability of two schedules of i.v. irinotecan with intermittent capecitabine given as first-line therapy in patients with metastatic CRC.

MATERIALS AND METHODS

Patient Eligibility

Patients who had not received previous chemotherapy for metastatic CRC were considered eligible for study entry. Any previous adjuvant chemotherapy must have been completed $\geq$ 6 months before enrolment. Histologic confirmation of colorectal adenocarcinoma

was required, as was the presence of at least one unradiated, unidimensionally or bidimensionally measurable lesion using computed tomography scans (CT), magnetic resonance imaging scans (MRI), or X-rays. The patients had to be ages 18–70 years and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 or, if older, an ECOG performance status of 0–1.

The other eligibility criteria were an absolute neutrophil count of $\geq 2.0 \times 10^9$/L; a platelet count $\geq 100 \times 10^9$/L; hemoglobin level $\geq$ 10 g/dL; serum creatinine level $\leq$ 1.25 mg/dL; serum bilirubin level $\leq$ 1.5 times the upper normal limit (UNL); and alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase $<$ 2.5 times the UNL. However, up to five times the UNL for alkaline phosphatase, ALT, and AST was allowed in patients with liver metastases and up to 10 times the UNL for alkaline phosphatase in patients with bone metastases.

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki and written informed consent was obtained from all of the patients. The study protocol was approved by the ethics committees of the participating centers, as were all of the necessary amendments.

Women of childbearing potential were required to adopt contraceptive measures, whereas pregnant or lactating patients were excluded. The other exclusion criteria were patients with a history of other cancers (except patients with complete remission of basal cell skin carcinoma or in situ carcinoma of the uterine cervix) and patients who had not fully recovered from recent major surgery (within the previous 4 weeks); the presence of organ allografts, central nervous system involvement, or a liver lesion $>$ 50% of the organ; neurologic or psychiatric disorders, which may interfere with treatment compliance; severe cardiac disease or a myocardial infarction within the previous 12 months; uncontrolled metabolic disorders; active serious infections; and inflammatory bowel disease, bowel obstruction, or a history of chronic diarrhea or malabsorption syndrome.

Study Design and Treatments

This open-label, multicenter, randomized Phase II trial was conducted by the Italian Trials in Medical Oncology (ITMO) group and coordinated by Medical Oncology Unit B, Istituto Nazionale per lo Studio e la Cura dei Tumori (Milan, Italy). The eligible patients from 14 Italian centers were randomly assigned to receive two schedules of irinotecan in combination with capecitabine.

The patients were centrally randomized to the study treatments by the ITMO scientific office after the clinical investigator had telephoned the data manager and the inclusion and exclusion criteria had been checked. Randomization was based on a computer-generated randomization list, stratified by center. The procedure was performed in such a way that the investigators did not know the allocation before it was made.

The treatment was comprised of capecitabine administered twice daily at an oral dose of 1250 mg/m^2 (equivalent to a total dose of 2500 mg/m^2 per day) on Days 2–15 and irinotecan given at a dose of 300 mg/m^2 on Day 1 (Arm A) or 150 mg/m^2 on Days 1 and 8 (Arm B). The cycles were repeated every 3 weeks. The protocol specified that, if Grade 3–4 diarrhea was observed in $\geq$ 33% of the planned patients, the doses of both drugs had to be reduced by 20%. On the basis of the results of an interim analysis, enrollment was continued using lower doses of irinotecan (Arm A, 240 mg/m^2; Arm B, 120 mg/m^2) and capecitabine (1000 mg/m^2 twice daily) administered using the same treatment schedules. The capecitabine doses were rounded to the nearest dose that could be administered using 500-mg and 150-mg tablets. The drug was taken orally with water at 12-hour intervals within 30 minutes of food ingestion. Irinotecan was administered as an i.v. infusion over 90 minutes. The combination treatment was continued for a maximum of 10 cycles in patients with an objective response or until the development of disease progression if earlier.

Efficacy and Safety Analyses

Tumor size (minimum of 15 mm in at least 1 dimension) was assessed using CT and MRI scans or X-rays before the initiation of treatment, after every three therapeutic cycles, and at the end of treatment. Complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) were defined on the basis of the standardized response definitions of the World Health Organization (WHO).[38] Safety evaluations, including the clinical assessment of any adverse events and laboratory parameters, were made during each treatment cycle (after 21 days in Arm A and after 8 days in Arm B) and then until 21 days after the first day of chemotherapy. The intensity of clinical adverse events was graded using the NCIC-CTC grading system (version 2.0). The adverse events not listed by the NCIC-CTC grading system were considered mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Hand-foot syndrome (HFS; or palmar-plantar erythrodysesthesia) was classified as Grade 1 (numbness, dysesthesia, painless swelling, or erythema not disrupting normal activity), Grade 2 (painful erythema with swelling or affecting daily living activities), or Grade 3 (moist des-

quamation, ulceration, blistering or severe pain, or any symptoms leading to an inability to work or to perform daily living activities). Complete blood counts were obtained before each administration of irinotecan.

Treatment Modifications

No treatment interruptions or dose reductions were indicated for reactions that were unlikely to become serious or life-threatening or for Grade 1 toxicity. Treatment was interrupted for patients with Grade 2 toxicity or worse and resumed once the adverse event had resolved or improved to Grade 0–1. When patients experienced hematologic toxicities other than neutropenia (e.g., leukopenia, anemia, or thrombocytopenia) or diarrhea, a new course of therapy could not begin until the granulocyte count had returned to $\geq 1.5 \times 10^9$/L, the platelet count had returned to $\geq 100 \times 10^9$/L, and the treatment-related diarrhea had fully recovered. Treatment was delayed for 1–2 weeks to allow for recovery. The dose was reduced by 25% for patients experiencing a second occurrence of a Grade 2 toxicity or any Grade 3 toxicity and by 50% for patients experiencing a third occurrence of a Grade 2 toxicity, a second occurrence of a given Grade 3 toxicity, or any occurrence of Grade 4 toxicity. Treatment was discontinued in patients experiencing a fourth Grade 2 toxicity, a third Grade 3 toxicity, or a second Grade 4 toxicity.

To ensure that the patients adequately complied with their treatment regimen, the medication returned at each visit was checked, counted, and recorded in the drug-dispensing log. Patients who stopped treatment for >1 week for reasons other than toxicity were withdrawn from the trial because of noncompliance.

Statistical Analysis

The primary efficacy end point was the objective response rate, including CR and PR. In the trial planning phase, we used the Simon approach to optimal 2-stage design and estimated that 55 patients were required in each treatment arm to reject the null hypothesis of a 15% baseline response rate at a 10% significance level and 90% power for a 15% improvement under the alternative hypothesis (15–30%).[39] The threshold for rejecting the null hypothesis was a maximum of 11 responses among the total of 55 patients. However, as the actual sample size exceeded the planned number, the rejection thresholds were suitably adjusted before analysis. Although no direct between-group comparison of response rates was planned, computer- generated lists (stratified by center) were used to randomize the individual patients to one of the two treatment arms.

For exploratory purposes, we investigated the effect of treatment dose on the response rate by means of the Cochran–Mantel–Haenszel test, stratifying the analysis by treatment arm. The effects of patient age, disease extension, and lactate dehydrogenase (LDH) levels were also investigated using the same test, stratifying the analysis by treatment arm and dose.

The time to tumor progression was calculated from the date of randomization to the first recorded observation of progression, the date of last contact, or death. Progression-free survival curves were calculated using the Kaplan–Meier method.

The safety assessment considered the frequency of observed adverse events. The association between the occurrence of adverse events and the treatment schedule or dose was investigated by means of the Cochran–Mantel–Haenszel test, using dose as the stratification factor when analyzing the treatment schedule or vice versa. All of the given P values are two sided.

The efficacy analysis was based on all of the patients receiving treatment except those who were treated for < 9 weeks because of death, PD, or adverse events. The patients with no postbaseline tumor assessment were classified as nonresponders or treatment failures. The duration of response was calculated according to the WHO response criteria and was based on all responding patients.

The patients who did not receive at least one dose of study medication were excluded from the safety analysis.

RESULTS

Between July 1999 and August 2001, 145 patients were randomized. Five patients were excluded from the analysis as they did not receive study treatment because of the following early events: lost to follow-up ($n = 1$), staphylococcal sepsis ($n = 1$), death ($n = 2$), and cardiac disorder ($n = 1$). The demographic and baseline data relating to the remaining 140 patients (71 in Arm A, 69 in Arm B) are shown in Table 1. The two groups were generally well matched in terms of gender, age, ECOG performance status, the localization and number of metastatic sites, and altered carcinoembryonic antigen or LDH levels. However, previous adjuvant chemotherapy had been administered more frequently to the patients in Arm A (37%) compared with Arm B (19%). A high proportion of patients had undergone previous radical surgery of the primary tumor (71% in Arm A, 75% in Arm B) and a small number had received radical surgery for metastatic lesions (9% in Arm A, 5% in Arm B). The first 52 patients (28 in Arm A, 24 in Arm B) received high-dose capecitabine and irinotecan treatment, whereas the

TABLE 1
Baseline Demographic, Disease, and Previous Therapy Characteristics

Characteristics	Arm A (n = 71) (%)	Arm B (n = 69) (%)	Total (n = 140) (%)
Males	45 (63)	42 (61)	87 (62)
Females	26 (37)	27 (39)	53 (38)
Median age (range)	61 (40–75)	60 (33–75)	61 (33–75)
ECOG PS			
0–1	68 (96)	67 (97)	135 (96)
2	3 (4)	2 (3)	5 (4)
Primary tumor			
Colon	49 (69)	46 (67)	95 (68)
Rectum	22 (31)	23 (33)	45 (32)
Median between first diagnosis and randomization (days) (range)	71 (3–3421)	62 (3–3032)	64 (3–3421)
Altered CEA level (> 10 ng/mL)	50 (76)	53 (79)	103 (77)
Unknown	5	2	7
No. of sites			
1	12 (17)	11 (16)	23 (16)
≥ 2	59 (83)	58 (84)	117 (84)
Organs involved			
Liver and lung	30 (42)	32 (46)	62 (44)
Liver	6 (8)	9 (13)	15 (11)
Lung	4 (6)	—	4 (3)
Lung, liver, other[a]	31 (28)	28 (40)	59 (42)
Previous adjuvant chemotherapy	26 (37)	13 (19)	39 (28)
Abnormal LDH level	19 (32)	18 (30)	37 (31)
Median LDH (range)[b]	1.34 (1.01–3.38)	1.31 (1.01–4.86)	1.35 (1.01–4.86)
Unknown	12	8	20

ECOG Eastern Cooperative Oncology Group; PS: performance status; CEA: carcinoembryonic antigen; LDH: lactate dehydrogenase.

[a] Other: rachis, kidney, abdomen, and lymph nodes.

[b] Values are standardized over the upper normal limit.

remaining 88 patients (43 in Arm A, 45 in Arm B) received low-dose treatment. Adherence to treatment was satisfactory. For example, a median of 6 treatment cycles were administered overall (8 in Arm A, 6 in Arm B) and 19% of the patients received 10 cycles (Arm A, 25%; Arm B, 13%). Only 11 patients in Arm A and 15 patients in Arm B were treated with fewer than 3 cycles because of early progression (2 in both arms), death (1 in Arm A, 3 in Arm B), adverse events (5 in Arm A, 7 in Arm B), or refusal/poor compliance (3 in both groups).

TABLE 2
Efficacy Analysis of 134 Patients

Parameters	Arm A (n = 68) (%)	Arm B (n = 66) (%)
Overall response	32 (47)	29 (44)
Complete	6 (9)	5 (8)
Partial	26 (38)	24 (36)
Stable disease	23 (34)	14 (21)
Failures[a]	13 (19)	23 (35)

[a] Including patients who were withdrawn early because of side effects or death.

Objective Responses and Time to Progression

After the exclusion of 6 patients who discontinued treatment before the first evaluation due to refusal (n = 5) or poor compliance (n = 1), 134 patients were evaluable for efficacy. Overall, 61 of 134 patients (46%) achieved an objective response: 11 CRs (8%) and 50 PRs (37%; Table 2). The objective response rate was similar in the 2 arms: 47% in Arm A (95% confidence interval [CI], 35–60%) and 44% in Arm B (95% CI, 32–57%). The threshold number of responses to be observed for rejecting the null hypothesis (14 in Arm A and 13 in Arm B) was largely exceeded. The actuarial median response duration was 7 months (range, 1–8 months).

The responses were also evaluated according to treatment dose and major baseline characteristics. A higher response rate was observed in the patients receiving low-dose treatment (50% vs. 38%). This statistically nonsignificant finding (P = 0.1605) may be explained by the higher number of cycles (i.e., a median of nine cycles and six cycles in low-dose Arms A

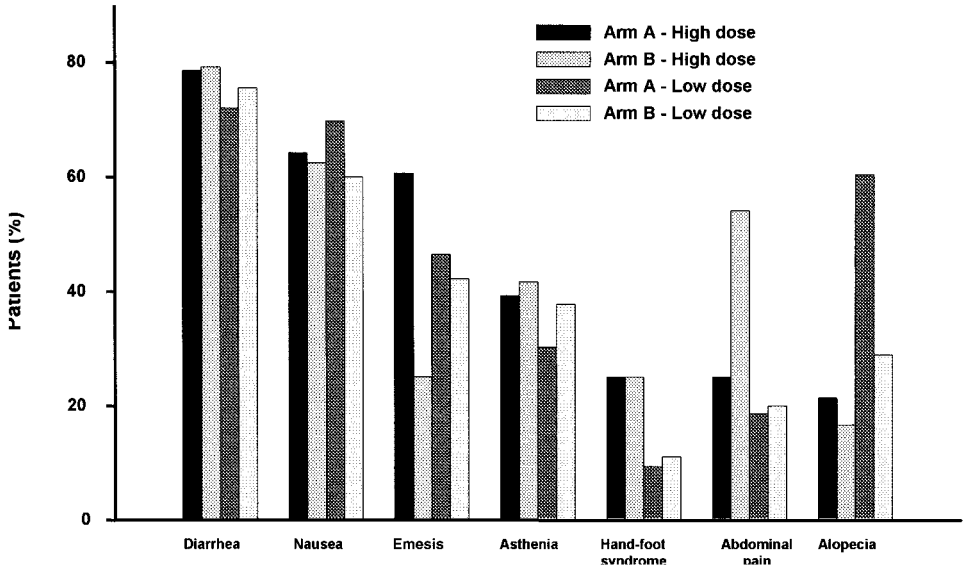

FIGURE 1. Frequency of adverse events (all grades) by treatment arm and dose.

TABLE 3
Grade 3–4 Nonhematologic Adverse Reactions[a]

	High dose		Low dose	
Parameters	Arm A (n = 28) (%)	Arm B (n = 24) (%)	Arm A (n = 43) (%)	Arm B (n = 45) (%)
Diarrhea	10 (35.7)	4 (16.7)	11 (25.6)	17 (37.8)
Nausea	3 (10.7)	3 (12.5)	5 (11.6)	4 (8.9)
Emesis	2 (7.1)	—	6 (14.0)	3 (6.7)
Asthenia	4 (14.3)	—	—	1 (2.2)
Hand-foot syndrome	4 (14.3)	—	—	1 (2.2)
Overall	15 (53.6)	5 (20.8)	14 (32.6)	19 (42.2)

[a] Grading was performed according to the second version of the National Cancer Institute, Common Toxicity Criteria.

and B, respectively, vs. six cycles and four cycles in high-dose Arms A and B, respectively).

The response rate was higher in the patients < 65 years (53%) compared with older patients (31%; $P = 0.0220$), but this difference did not lead to any advantage in terms of time to progression (hazard ratio, 0.996; 95% CI, 0.968–1.025). No significant association was found between the objective response rate and disease extension ($P = 0.3355$) or LDH levels ($P = 0.8211$). The median time to progression was 8.3 months in Arm A and 7.6 months in Arm B.

Side Effects

Of the 140 patients who received at least one cycle, all of those treated with high doses and 99% of those treated with low doses experienced at least 1 adverse event. Figure 1 shows the frequency of all-grade adverse reactions reported by $\geq 15\%$ of the patients, by treatment group and dose level. These two factors had no significant effect on the occurrence of diarrhea, nausea, emesis, or asthenia. However, significant reductions in the incidence of HFS ($P = 0.0209$) and abdominal pain ($P = 0.0105$) were associated with the use of low-dose treatment, and the opposite was true for alopecia.

Table 3 shows the frequencies of the most important Grade 3–4 nonhematologic adverse events. The occurrence of Grade 3–4 diarrhea in $> 33\%$ of the patients planned to receive the high-dose regimen led to the application of the 20% dose reduction foreseen in the protocol. Overall toxicity was particularly frequent in the high-dose Arm A (53.6%), mainly due to diarrhea (35.7%). The subsequent dose modification made on the basis of this finding led to better control of diarrhea, asthenia, and HFS, but statistical analysis did not reveal any significant overall dose effect ($P = 0.9383$).

Hematologic toxicity decreased after the dose reduction. Hematologic toxicity occurred in approxi-

mately 10% of patients ($P = 0.0892$) and neutropenia occurred in approximately 5% of patients.

Grade 3–4 side effects occurred more frequently in patients ≥ 65 years. Diarrhea was reported in 32% of the patients in Arm A and in 42.7% of the patients in Arm B, whereas leukopenia was observed in 12% of the patients in Arm A and in 8.3% of the patients in Arm B. The incidence of side effects in this subset of older patients was not decreased by lowering the doses of capecitabine and irinotecan (data not shown).

Adverse reactions led to dose reductions or temporary treatment interruptions in 77 patients (55%; 49% in Arm A and 61% in Arm B). In this patient subset, the dose reductions regarded capecitabine in 83% of patients (71% in Arm A, 94% in Arm B) and irinotecan in 90% of patients (81% in Arm A, 97% in Arm B). The treatment was discontinued in 43 patients (31%; 27% in Arm A and 35% in Arm B) because of PD, in 21 patients (15%; 15% in Arm A and 14% in Arm B) because of adverse reactions, in 13 patients (9.3%) because of consent withdrawal, and in 5 patients (3.5%; 2.8% in Arm A and 4.3% in Arm B) because of death. In particular, one patient in Arm B and one in Arm A died of myocardial infarction. The patient in Arm B was 54 years old and had Type II diabetes, and the event was reported 68 days after the initiation of treatment, whereas the patient in Arm A was 68 years old, had a history of previous myocardial infarction and increased cardiac risk, and died 76 days after the initiation of treatment. A 72-year-old patient in Arm B treated with 1 cycle died of a gastrointestinal syndrome caused by treatment-induced Grade 4 diarrhea. The remaining 2 Arm B patients died of a cerebrovascular accident occurring 59 days after the initiation of treatment and a suspected pulmonary embolus originating from deep venous thrombosis.

DISCUSSION

In the the current randomized Phase II study, i.v. irinotecan in combination with standard, intermittent oral capecitabine as first-line therapy in patients with metastatic CRC led to an overall response rate of 46%, including CR in 11 patients (8%) and PR in 50 patients (37%). No clear difference in response rates or time to progression-free survival was observed between the two arms, although more patients in Arm A had SD.

The adverse event profile during the study was qualitatively similar in Arms A and B, with gastrointestinal disturbances (including diarrhea, nausea, and emesis) being the most frequent events. Lowering the doses of irinotecan and capecitabine reduced the occurrence of Grade 3–4 diarrhea, asthenia, HFS, and hematologic adverse events (neutropenia, leukopenia, and anemia) in the patients in Arm A, whereas the patients in Arm B did not benefit from the dose reductions. The apparently superior adverse event profile in Arm A was reflected in its lower rate of dose reductions or temporary treatment interruptions. In addition, the median number of administered cycles was also higher in Arm A compared with Arm B.

A subset analysis of the elderly patients indicated that the dose reduction failed to control the gastrointestinal side effects. Therefore, we recommend that this regimen should only be used in patients without comorbidities. Improved criteria need to be developed for the treatment of patients > 65 years.

Our efficacy findings support the reported preliminary results of a number of Phase I/II studies of combined irinotecan and capecitabine therapy indicating overall response rates of 41–52%.[40,41] Our findings also agree with those of two large randomized trials of bolus 5-FU or infusional 5-FU plus irinotecan as first-line treatment indicating response rates of 39–49%.[26,27] The types of adverse reactions observed in our study are also consistent with the known profiles of continuous 5-FU infusion regimens and irinotecan, including the lower incidence of Grade 3–4 neutropenia (5% vs. 46%), despite the increase in Grade 3–4 diarrhea (25.6% vs. 14%).[26]

The results could serve as the basis for identifying the experimental arm in a Phase III comparison with the Douillard regimen. Moreover, in combination with capecitabine, the single-dose administration of irinotecan may be effective and better tolerated than the use of two divided doses.

Other ongoing trials are currently evaluating combinations of capecitabine and oxaliplatin, capecitabine and radiotherapy, and a combination of oral capecitabine plus oral irinotecan.[42,43] The results of these trials, together with an appropriate clinical economic and quality of life study, will determine whether capecitabine can replace 5-FU, particularly when used in conjunction with other highly active anticancer agents such as irinotecan.

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