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Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer, an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) phase III study

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Background: Results on overall survival in randomised studies of mono- versus combination chemotherapy in advanced colorectal cancer patients may have been biased by an imbalance in salvage treatments. This is the first randomised study that evaluates sequential versus combination chemotherapy with a fluoropyrimidine, irinotecan and oxaliplatin.

Patients and methods: A total of 820 patients were randomised between first-line capecitabine, second-line irinotecan and third-line capecitabine + oxaliplatin (arm A) versus first-line capecitabine + irinotecan, and second-line capecitabine + oxaliplatin (arm B). The primary end point was overall survival. We present the results of an interim analysis on the safety data in the first 400 patients.

Results: In first-line the incidence of grade 3–4 diarrhoea, nausea, vomiting and febrile neutropenia was significantly higher in arm B. However, when toxicity over all lines was considered only grade 3 hand–foot syndrome occurred more frequently in arm A (12% versus 6%, respectively, $P = 0.041$). The incidence of cardiovascular toxicity was low. In two out of five patients with sudden death (one in arm A, four in arm B) cardiovascular risk factors were present.

Conclusions: Both treatment arms had an acceptable safety profile. These data imply that the results on survival will be the major determinant for the selection of either strategy. Capecitabine plus irinotecan appears to be a feasible first-line treatment for patients with advanced colorectal carcinoma.

Key words: advanced colorectal cancer, capecitabine, chemotherapy, irinotecan, oxaliplatin, safety

introduction

The systemic treatment of advanced colorectal cancer has changed considerably over the past decade and the prognosis of patients has improved significantly by the availability of the cytotoxic drugs irinotecan and oxaliplatin [1]. A retrospective analysis has shown that the median overall survival is increased when all three active drugs [5-fluorouracil/leucovorin (5-FU/LV), irinotecan and oxaliplatin] are made available to patients with advanced CRC [2]. Several studies have shown a statistically significant benefit in overall survival for the combination of irinotecan and 5-FU over treatment with 5-FU alone [3, 4], and the combination of oxaliplatin with infusional 5-FU was shown to be superior to irinotecan plus bolus 5-FU [5]. However, salvage treatment was not a prospective part in any of these studies and the suboptimal use of effective salvage treatment in the control arms has probably influenced the outcome of these studies [1]. Therefore it has not been unequivocally shown that combination treatment is superior compared with the sequential use of these drugs, which may be relevant since combination treatment is likely to be accompanied with more toxicity. The UK FOCUS study [6] compares sequential versus combination treatment for either irinotecan or oxaliplatin with 5-FU/LV in separate treatment arms. A study amendment later advised the continuation of

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oxaliplatin after exposure to irinotecan and vice versa, but this was not a mandatory, integral part of the study and preliminary data showed that only a small percentage of patients was exposed to all three cytotoxic drugs.

Our study is the first randomised phase III study that prospectively evaluates the sequential versus the concomitant use of all three effective cytotoxic agents. Current data do not suggest a preferred sequence of irinotecan and oxaliplatin [7] and our choice for irinotecan as first-line treatment was only made because at the time the study started irinotecan was used more frequently in The Netherlands. The use of oral capecitabine has shown improved safety and at least equivalent efficacy when compared with intravenous 5-FU/LV [8, 9]. Phase II studies [10, 11] and a recent phase III interim analysis [12] have shown comparable efficacy for capecitabine versus 5-FU when used in combination with either irinotecan or oxaliplatin. We here present the results of an interim safety analysis of the sequential versus combined use of capecitabine, irinotecan and oxaliplatin. These are especially relevant in the light of the results of the EORTC 40015 phase III study that was closed prematurely due to the occurrence of severe toxicity in patients treated with the same regimen of capecitabine plus irinotecan [13].

patients and methods

patients

The main eligibility criteria were histological proof of colorectal carcinoma, advanced disease not amenable to curative surgery, measurable or evaluable disease parameters, no previous systemic treatment except for adjuvant chemotherapy provided that the last administration was given ≥6 months prior to randomisation, age ≥18 years, WHO performance score 0–2, written informed consent, adequate bone marrow function (white blood cells $\geq 3.0 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, haemoglobin ≥6 mmol/l); adequate hepatic function [total bilirubin ≤1. 5 × upper limit of normal (ULN), ASAT and ALAT ≤3 × ULN; in case of liver metastases ≤5 ×ULN]; adequate renal function: calculated creatinin clearance >50 ml/min (Cockcroft–Gault formula). The main exclusion criteria were serious concomitant disease preventing the safe administration of chemotherapy, symptomatic CNS metastases, or other malignancies in the past 5 years with the exception of adequately treated carcinoma *in situ* of the cervix or squamous/basal cell carcinoma of the skin. Ineligible patients and patients with missing data or consent withdrawal were excluded of all analysis. Patients who never started treatment were excluded from the safety analysis, but included in the mortality analysis.

The study was conducted in accordance with the standards of good clinical practice and in agreement with the Declaration of Helsinki, and was approved by the national Central Committee on Research Involving Human Subjects (CCMO). Patients who were randomised in the first year of the study were included in this analysis.

study design

This was a multicentre, randomised phase III trial. The primary end point was overall survival, the secondary objective was to evaluate and assess tumour response, progression-free survival, quality of life and safety.

Data collection was performed by the regional Comprehensive Cancer Centres (Nederlandse Integrale Kanker Centra, IKC). Patients were centrally randomised through adaptive minimisation at the Netherlands Cancer Institute (NKI) to one of the treatment arms. Central data management was performed at the Comprehensive Cancer Centre East (IKO). Data analysis was done at the department of Biostatistics of the Netherlands Cancer Institute. Patients were stratified according to WHO performance status (0–1 versus 2), serum LDH (normal versus above normal), prior adjuvant therapy (yes versus no), predominant localisation of metastases (liver versus extrahepatic sites) and per participating institution. Treatment was to be initiated within 7 days after randomisation. An independent data monitoring committee (IDMC) continuously evaluated all serious toxicity.

treatment

Arm A consisted of first-line capecitabine, second-line irinotecan and third-line capecitabine plus oxaliplatin. Arm B consisted of first-line capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin (Figure 1). All cycles were administered every 3 weeks. Capecitabine was administered from day 1–14 bid, 1250 mg/m^2 (monotherapy) or 1000 mg/m^2 (in combination with irinotecan or oxaliplatin). Irinotecan was administered on day 1 of each cycle at 350 mg/m^2 (monotherapy) or 250 mg/m^2 (in combination with capecitabine) and oxaliplatin on day 1 at 130 mg/m^2. Treatment was continued until disease progression, unacceptable toxicity or patient refusal, whichever came first.

Clinical and laboratory toxicity were graded according to NCI-CTC version 2.0. The causality between toxic events and study drugs was graded as not related, remote, possible or probable. Dose reductions for grade 2–4 toxicity were performed for capecitabine as described previously [9]. A 25% dose reduction was performed for irinotecan or oxaliplatin for any grade 3–4 toxicity and for oxaliplatin also for persistent (≥14 days) paresthesias or temporary (7–14 days) painful paresthesias. Since age >70 years, WHO performance status 2 and/or serum bilirubin between 1 and 1.5 × ULN have been associated with an increased risk for irinotecan-related toxicity, it was recommended to treat patients with one or more of these characteristics with a 20% dose reduction of irinotecan during cycle 1. If this was well tolerated the dose of irinotecan was to be escalated to 100% in the second and subsequent cycles. The following evaluations were performed at every 3-weekly follow-up visit: clinical examination, residual toxicity due to prior therapy, disease symptoms, performance status, and laboratory tests (haematology and biochemistry). Assessment of tumour response was scheduled every three cycles (9 weeks). Follow-up after completion of treatment was done every 3 months until death.

statistical analysis/interim safety analysis

All analyses were done by intention to treat principle. Safety evaluation was performed by patient and by treatment line on all eligible patients. Comparisons of distribution and rates of toxicity were done using the chi-squared test. This safety analysis was performed in the patients included during the first year of the study (n = 400). The main objectives were to evaluate the toxicity profile, to compare the toxicity with a probable or possible relation to the study drug of corresponding treatment lines and to

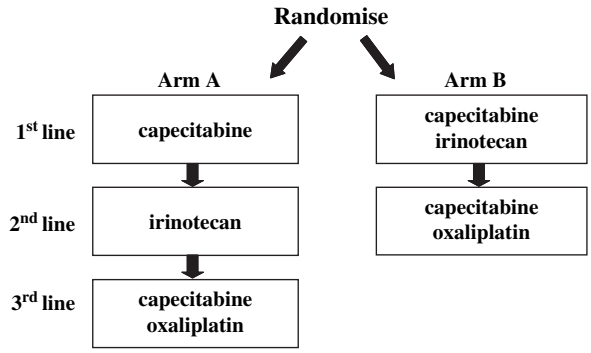

Figure 1. Study design.

compare the overall toxicity between sequential versus combination therapy. The charts of all patients who died within 30 days of the last administration of study drugs and whose death was not being reported as due to disease progression, were reviewed by the principal investigator.

results

A total of 820 patients were randomised in 74 hospitals from 1 January 2003 to 1 January 2005. By 7 March 2006, of the first 400 randomised patients a total of 389 eligible patients were known to have entered the first-line treatment period and 214 patients the second-line treatment period. Median follow-up of this cohort of patients was 23.2 months.

Seven patients were found to be ineligible, one patient in arm A and six patients in arm B. Reasons for ineligibility were: no evaluable target lesions ($n = 1$), no histological proof of colorectal carcinoma ($n = 1$), serious concomitant disease or laboratory parameters beyond ULN preventing the safe administration of study drugs ($n = 5$). Two patients were excluded from the mortality and safety analysis for missing data ($n = 1$) and withdrawal of informed consent ($n = 1$). Two patients never started treatment and were therefore not evaluable for toxicity, but were included in the mortality analysis. A total of 198 evaluable patients started first-line treatment in arm A and 191 patients in arm B. Characteristics of eligible patients were well balanced and are shown in Table 1.

Table 1. Patient characteristics

Characteristics	Arm A $n = 199$	Arm B $n = 194$	Total $n = 393$
Age (years)			
Median	64.0	63.0	63.0
Range	27–84	35–79	27–84
Gender			
Male	124 (63%)	116 (60%)	240 (61%)
Female	74 (37%)	76 (39%)	150 (38%)
Missing	1 (<1%)	2 (1%)	3 (<1%)
WHO performance status			
0	122 (61%)	111 (57%)	233 (59%)
1	66 (33%)	73 (38%)	139 (35%)
2	11 (6%)	10 (5%)	21 (5%)
Serum LDH			
Normal	133 (67%)	127 (65%)	260 (66%)
>ULN	66 (33%)	67 (35%)	133 (34%)
Prior adjuvant therapy			
No	170 (85%)	164 (85%)	334 (85%)
Yes	29 (15%)	30 (15%)	59 (15%)
Localisation of metastases			
Liver	131 (66%)	131 (68%)	262 (67%)
Extrahepatic sites	65 (33%)	62 (32%)	127 (32%)
Unknown	3 (2%)	1 (<1%)	4 (1%)
Site of primary tumour			
Colon	86 (43%)	86 (44%)	172 (44%)
Rectum	61 (31%)	59 (30%)	120 (31%)
Rectosigmoid	49 (25%)	46 (24%)	95 (24%)
Missing	3 (2%)	3 (2%)	6 (2%)

toxicity

Toxicity results are summarized in Tables 2 and 3. In first-line the most important grade 3–4 toxicities in arm A versus B were: all grades cholinergic syndrome (0% versus 19%, $P \leq 0.0001$), hand–foot syndrome (11% versus 5%, $P = 0.020$), diarrhoea (9% versus 23%, $P = 0.0001$), nausea (3% versus 9%, $P = 0.009$), vomiting (3% versus 9%, $P = 0.003$) and febrile neutropenia (<1% versus 6%, $P = 0.002$) (Table 2).

In second-line there was a significant difference in the incidence of cholinergic syndrome (29% versus 0%, $P \leq 0.0001$), all grades hypersensitivity reactions (<1% versus 8%, $P = 0.010$) and sensory neuropathy (<1% versus 6%, $P = 0.022$) between treatment with irinotecan (arm A) versus treatment with capecitabine plus oxaliplatin (arm B). Other important differences in the observed frequencies of adverse events were found for diarrhoea (17% versus 8%, $P = 0.049$) and febrile neutropenia (7% versus 1%, $P = 0.046$).

When toxicity over all lines was considered, no statistically significant difference was observed for haematological and non-haematological toxicity between both treatment arms except for the incidence of grade 3 hand–foot syndrome, which occurred more frequently in arm A (12% versus 6%, $P = 0.041$). The incidence of cardiac ischaemia/infarction (2% versus 2%) and thrombo-embolic events (4% versus 6%) was comparable between arms A and B, respectively (Table 3).

mortality

By 7 March 2006 248 patients of 391 eligible and evaluable patients were known to have died. In seven patients a causative role between death and the study treatment is considered probable, five in arm A and two in arm B (Table 4). In five of these seven patients a major protocol violation was detected after review of the hospital charts: in two patients irinotecan was administered with hyperbilirubinaemia grade 3 at baseline and in three patients capecitabine was continued at full dose after or during grade 3 diarrhoea. Both patients with hyperbilirubinaemia had a normal bilirubine before and during previous first-line treatment with capecitabine monotherapy until progression was diagnosed.

In eight patients a relation between the study drug and death was considered possible, two in arm A and six in arm B (Table 5). Sudden death was the cause of death in five patients, one during the first cycle of third-line treatment in arm A and four during the second cycle of first-line treatment in arm B. In two of these patients cardiovascular risk factors were present. Other causes of death were pulmonary embolism in a patient with a history of supraventricular tachycardia, vomiting and dehydration due to disregulation of diabetes mellitus, and cardiac failure in a patient with a cardiovascular history.

discussion

Our interim results on safety show that combination treatment does not give rise to a higher overall incidence of toxicity compared with sequential therapy. This may be explained by the fact that a high percentage of patients were eventually exposed to all three study drugs. When all treatment lines were considered there were no significant differences of toxicity

Table 2. Toxicities of first-line treatment

Non-haematological adverse events	Arm A $n = 198$	Arm B $n = 191$	Total $n = 389$	P value[a]
Cholinergic syndrome, total	0 (0%)	37 (19%)	37 (10%)	<0.0001
Hypersensitivity reaction, total	5 (3%)	3 (2%)	8 (2%)	0.507
Cardiac ischaemia/infarction, total	3 (2%)	4 (2%)	7 (2%)	0.668
Thrombosis/embolism, total	5 (3%)	12 (6%)	17 (4%)	0.070
Fatigue (lethargy, malaise, asthenia)				
Grade III	9 (5%)	15 (8%)	24 (6%)	0.175
Hand–foot skin reaction				
Grade III	22 (11%)	9 (5%)	31 (8%)	0.020
Diarrhea				
Grade III	15 (8%)	38 (20%)	53 (14%)	0.0001
Grade IV	3 (2%)	6 (3%)	9 (2%)	
Nausea				
Grade III	6 (3%)	18 (9%)	24 (6%)	0.009
Stomatitis				
Grade III	2 (1%)	5 (3%)	7 (2%)	0.286
Grade IV	0	1 (<1%)	1 (<1%)	
Vomiting				
Grade III	3 (2%)	16 (8%)	19 (5%)	0.003
Grade IV	1 (<1%)	1 (<1%)	2 (<1%)	
Haematological adverse events				
Febrile neutropenia				
Grade III	1 (<1%)	10 (5%)	11 (3%)	0.002
Grade IV	0	2 (1%)	2 (<1%)	
Anaemia				
Grade III/IV	0	0	0	
Neutropenia				
Grade III	0	1 (<1%)	1 (<1%)	0.308
Grade IV	0	0	0	
Thrombocytopenia				
Grade III/IV	0	0	0	

[a]P values are presented for grade 3 and 4 toxicities combined.

in sequential treatment compared with combination treatment, except for grade 3 hand–foot syndrome occurring more frequently in arm A (12% versus 6%, respectively). The administration of a higher dose of capecitabine when given as monotherapy in sequential treatment is the most likely explanation of this difference. When only the toxicity in first-line is considered, treatment with capecitabine plus irinotecan resulted in a significantly higher incidence of grade 3–4 diarrhoea, nausea, vomiting, febrile neutropenia and all grades cholinergic syndrome, but less grade 3 hand–foot syndrome compared to treatment with capecitabine alone.

When we compare our results with previously published data from related studies several comments can be made. Our safety results for capecitabine monotherapy are in line with data from other phase III trials [8, 9]. The incidence of severe toxicity with capecitabine plus irinotecan in our study is comparable with the phase II results of the same schedule [10], with grade 3–4 diarrhoea as the most commonly occurring toxicity (23% versus 19%, respectively). The incidence of grade 3–4 diarrhoea in phase III studies with infusional 5-FU plus irinotecan was somewhat lower (13%) in a 2-weekly regimen and higher (44%) with a weekly regimen [4]. The incidence of febrile neutropenia was quite comparable among these studies. The low incidence of grade 3–4 neutropenia that we observed may be explained by the fact that haematological toxicity was only assessed at intervals of 3 weeks, implying that we did not record asymptomatic neutropenia, which is usually of low clinical relevance.

Our results are in contrast to the results of EORTC study 40015, in which infusional 5-FU was compared with capecitabine, both in combination with irinotecan and celecoxib versus placebo in a 2×2 factorial design. This study showed a high incidence of grade 3–4 diarrhoea with the same schedule of capecitabine plus irinotecan of 39% versus 7% in the control arm with a 2-weekly regimen of infusional 5-FU plus irinotecan [13]. This study was closed prematurely because of eight fatal events (9.4% of all randomised patients) of which six occurred in patients treated with capecitabine plus irinotecan (13.6%). The authors concluded that combination therapy with capecitabine and irinotecan at this dose and schedule is not feasible. Our results in a much larger cohort of patients do not confirm these findings. We observed a probable or possible relationship with capecitabine plus irinotecan in eight deaths (4%), which included a major protocol violation in one patient.

Table 3. Toxicities in all treatment lines

Non-haematological adverse events	Arm A $n = 198$	Arm B $n = 191$	Total $n = 389$	P value[a]
Cholinergic syndrome, total	38 (19%)	38 (20%)	76 (20%)	0.861
Hypersensitivity reaction, total	11 (6%)	10 (5%)	21 (5%)	0.889
Cardiac ischaemia/infarction, total	4 (2%)	4 (2%)	8 (2%)	0.276
Thrombosis/embolism, total	8 (4%)	12 (6%)	20 (5%)	0.364
Fatigue (lethargy, malaise, asthenia)				
Grade III	26 (13%)	20 (10%)	46 (12%)	0.440
Grade IV	2 (1%)	2 (1%)	4 (1%)	
Hand–foot skin reaction				
Grade III	23 (12%)	11 (6%)	34 (9%)	0.041
Diarrhea				
Grade III	31 (16%)	39 (20%)	70 (18%)	0.158
Grade IV	7 (4%)	8 (4%)	15 (4%)	
Nausea				
Grade III	15 (8%)	20 (10%)	35 (9%)	0.245
Grade IV		1 (<1%)	1 (<1%)	
Stomatitis				
Grade III	6 (3%)	5 (3%)	11 (3%)	0.829
Grade IV		1 (<1%)	1 (<1%)	
Vomiting				
Grade III	8 (4%)	17 (9%)	25 (6%)	0.105
Grade IV	3 (2%)	2 (1%)	5 (1%)	
Neuropathy sensory				
Grade III	2 (1%)	7 (4%)	9 (2%)	0.082
Haematological adverse events				
Febrile neutropenia				
Grade III	7 (4%)	11 (6%)	18 (5%)	0.335
Grade IV	2 (1%)	2 (1%)	4 (1%)	
Anaemia				
Grade III	1 (<1%)	1 (<1%)	2 (<1%)	0.583
Grade IV	1 (<1%)	0	1 (<1%)	
Neutropenia				
Grade III	0	1 (<1%)	1 (<1%)	0.308
Grade IV	0	0	0	
Thrombocytopenia				
Grade III	0	2 (1%)	2 (<1%)	0.971
Grade IV	2 (1%)	0	2 (<1%)	

[a]P values are presented for grade 3 and 4 toxicities combined.

The incidence of cardiac ischaemia/infarction and thrombo-embolic events in both arms was comparable and low. When all treatment lines were considered, five sudden deaths were observed among eight patients whose cause of death was considered possibly related to treatment. None of these deaths occurred during the first cycle of first-line treatment. This may argue against relationship with treatment, since the majority of fluoropyrimidine-related cardio-toxic events occur within the first cycle [14]. However, a possible relationship with study drugs cannot be excluded. Cardio-toxicity has been associated with fluoropyrimidine-containing regimens and a retrospective analysis did not show higher incidence upon treatment with capecitabine versus intravenous 5-FU/LV [14]. Our results confirm a cautious policy in treating patients with cardiovascular risk factors, but do not allow further specific recommendations.

After reviewing the charts of all deaths during treatment until 30 days after the last drug administration and whose death was not related to disease progression, we found a major protocol violation in five out of the seven deaths that were considered probably related to treatment. Two patients received second-line irinotecan with hyperbilirubinaemia grade 3 at baseline due to progression of disease and three patients received or continued full-dose capecitabine despite the occurrence of grade 3 diarrhoea. These data underline the necessity of adhering to specified protocol guidelines in order to prevent severe toxicity, and that a strict quality control is necessary for a true interpretation of safety results. Quality guidelines to prevent such protocol violations were discussed with the investigators involved in these incidents.

These interim results show that both sequential and combination treatment with capecitabine, irinotecan and

Table 4. Deaths in which a causative role of the study drug is considered probable

Patient	Arm	Line	Cycle no.	Days treatment (until death)	Event
1	A	First	4	7	Diarrhoea[a]
2	A	First	2	6	Neutropenic sepsis[a]
3	A	Second	2	1	Neutropenic sepsis[a]
4	A	Second	1	1	Neutropenic sepsis[a]
5	A	Second	2	13	Neutropenic sepsis
6	B	First	2	4	Neutropenic sepsis[a]
7	B	First	1	4	Neutropenic sepsis

[a]Major protocol violation.

Table 5. Deaths in which a causative role of the study drug is considered possible

Patient	Arm	Line	Cycle no.	Days treatment (until death)	Event
1	A	Second	1	21	Cardiac failure[a]
2	A	Third	1	1	Sudden death[a]
3	B	First	2	3	Pulmonary embolism[a]
4	B	First	2	12	Vomiting, dehydration[b]
5	B	First	2	2	Sudden death[a]
6	B	First	2	1	Sudden death
7	B	First	2	1	Sudden death
8	B	First	2	1	Sudden death

[a]Cardiovascular risk factors present.
[b]Due to disregulation of diabetes mellitus.

oxaliplatin is feasible and has an acceptable safety profile. In terms of safety our schedule of capecitabine plus irinotecan appears to be a useful alternative for other currently used regimens of a fluoropyrimidine and irinotecan, and the high mortality rate that has occurred in a recent EORTC trial with this schedule was not confirmed. However, the slight excess of sudden deaths in arm B compared with arm A is of some concern, but does not allow further conclusions.

This is the first phase III randomised study that prospectively compares sequential versus combination treatment with the three cytotoxic drugs that are widely used in the treatment of patients with advanced colorectal cancer. Grothey et al. [15] confirmed the survival benefit of patients receiving all three drugs in the updated pooled analysis on 5768 patients from 11 phase III trials regardless of whether doublet or single-agent therapy was used first line. Nevertheless, the patients who receive first-line chemotherapy doublets have a greater chance of receiving all three active agents in the course of their therapy as consistently approximately only 50%–60% of patients starting a line of therapy receive a next-line therapy, an observation that was confirmed in arm B of this study. At the time of this interim analysis treatment in many patients was still ongoing. This implies that the number of patients entering into second- or third-line treatment will increase with time. Final results on safety and survival are expected in 2007.

acknowledgements

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