ORIGINAL ARTICLE

Taylor&Francis healthsciences

A Phase II Study of UFT and Leucovorin in Combination with Mitomycin C in Patients with Metastatic Colorectal Cancer

Niels Gyldenkerne, Bengt Glimelius, Jan Erik Frödin, Mogens Kjaer, Per Pfeiffer, Flemming Hansen, Nina Keldsen, Erik Sandberg and Anders Jakobsen

From the Department of Oncology, Vejle Hospital, Vejle, Denmark (Niels Gyldenkerne, Anders Jakobsen), Department of Oncology, Akademiska Sjukhuset, Uppsala, Sweden (Bengt Glimelius), Department of Oncology, Radiumhemmet, Stockholm, Sweden (Bengt Glimelius, Jan Erik Frödin), Department of Oncology, Aalborg Sygehus, Aalborg, Denmark (Mogens Kjaer), Department of Oncology, Odense University Hospital, Odense, Denmark (Per Pfeiffer), Department of Oncology, Aarhus University Hospital, Aarhus, Denmark (Flemming Hansen), Department of Oncology, Herning Hospital, Herning, Denmark (Nina Keldsen) and Department of Oncology, Esbjerg Central Hospital, Esbjerg, Denmark (Erik Sandberg)

Correspondence to: Anders Jakobsen, Department of Oncology, Vejle Hospital, 7100 Vejle, DK-Denmark. Tel: +45 7940 5000. Fax: +45 7940 6856. E-mail: aja@vs.vejleamt.dk

Acta Oncologica Vol. 43, No. 3, pp. 276–279, 2004

The main objectives of this phase II study were to determine efficacy and safety of the combination of UFT with Leucovorin and mitomycin C in patients with metastatic colorectal cancer. Ninety-seven patients were treated with UFT (91 patients 300 mg/m^2, 6 patients 250 mg/m^2)+ Leucovorin 90 mg days 1–28 q 5 weeks. During the first 4 cycles the patients also received mitomycin C 7 mg/m^2 on day 1. At the end of 4 courses patients with benefit from the treatment could receive further courses of UFT and Leucovorin alone. Two patients had a complete response (2%), 20 (21%) had a partial response, 40 (41%) had no change, 19 (20%) had progression, and 16 (17%) were not evaluable for response. The overall response rate by intention to treat was 22/97 (23%). Median time to progression was 5 months and median survival 13 months. Severe (grade 3–4) toxicities included: anorexia 3%, nausea 6%, vomiting 7%, diarrhoea 7%, and fatigue 9%. Febrile neutropenia, renal failure, and thrombocytopenia were seen in 1% of the patients, respectively. The combination of UFT with Leucovorin and mitomycin C shows similar clinical activity with regard to overall response rate (23%) and survival (13 months) to other frontline 5-fluorouracil-based therapies in metastatic colorectal cancer patients. The results indicate that mitomycin C did not increase either efficacy or toxicity. Therefore, phase III trials with this regimen cannot be recommended.

Received 1 October 2003
Accepted 29 January 2004

Metastatic colorectal cancer represents a major therapeutic challenge in clinical oncology. Some patients with liver metastases can be offered resection with curative intent but the majority of patients are candidates for palliative chemotherapy. The cytotoxic treatment of metastatic colorectal cancer has changed considerably in recent years. The cornerstone is still 5-fluorouracil but combinations of 5-fluorouracil with new drugs, e.g. irinotecan and oxaliplatin, are more effective and combination chemotherapy is now considered standard in many institutions. However, the risk of serious toxic side effects has also increased with combination chemotherapy, and the challenge is still to find a reasonable balance between efficacy and toxic side effects, as cytostatic treatment is not curative in metastatic colorectal cancer.

Oral cytostatics represent a major advantage concerning quality of life (1). UFT is a combination of uracil and tegafur, a prodrug to 5-fluorouracil, in a molar ratio of 4:1. The rationale behind the drug is a competitive inhibition of dihydropyrimidine dehydrogenase and consequently a decreased catabolism of 5-fluorouracil. The drug shows an effect in metastatic colorectal cancer equal to that of 5-fluorouracil with regard to survival as shown in two large randomized trials (2, 3). It can be combined with new drugs in the treatment of metastatic colorectal cancer such as irinotecan and oxaliplatin if the dose of UFT is reduced (4, 5). It can also be combined with hydroxyurea (6) without any dose reduction.

Mitomycin C has been used in the treatment of colorectal cancer for several years (7, 8). Results in human cancer cell

 ISSN 0284-186X
DOI: 10.1080/02841860410028655

lines suggest a supra-additive effect of a combination of 5-fluorouracil and mitomycin C (9). Phase II studies also suggest an improved effect of the combination when 5-fluorouracil is given as a continuous infusion but this was not confirmed in phase II trials (10, 11) with 5-fluorouracil given as i.v. bolus. On the other hand the results of a phase III trial (12) indicated a better effect of the combination with 5-fluorouracil administered as a prolonged i.v. infusion.

The objective of the present study was to combine UFT and Leucovorin with mitomycin C in the treatment of metastatic colorectal cancer. The primary end point was response rate. The secondary endpoints were progression free survival, survival, and spectrum of toxic side effects.

MATERIAL AND METHODS

The study included 97 patients with metastatic colorectal cancer entered over the period March 2000–November 2000. The inclusion criteria were histologically confirmed colorectal adenocarcinoma with metastases and at least one measurable lesion located outside previously irradiated fields. Performance status 0–2, absolute neutrophile count $\geq$ than 1.5×10^9, platelet count $\geq 100 \times 10^9$, and informed consent according to the Helsinki II Declaration. Previous adjuvant treatment was allowed if it had been terminated ≥ 12 months before protocol entrance.

Patients with brain metastases or other malignant diseases were excluded. The same applied to patients receiving previous treatment for metastatic disease. Some patient characteristics are given in Table 1. It appears that almost 75% of the patients had liver metastases and 90% had performance status 0 or 1. The pre-treatment evaluation included a full history, physical examination, computerized tomography or abdominal ultrasound, chest x-ray and measurement(s) of the lesion(s) chosen for evaluation according to the WHO criteria.

The treatment course consisted of UFT 250 mg/m^2 and Leucovorin 90 mg days 1–28 q 5 weeks for the first 6 patients. With an acceptable safety profile the dose of UFT was increased to 300 mg/m^2. Ninety-one patients received 300 mg/m^2. Mitomycin C was given in a dose of 7 mg/m^2 on day 1 in the first 4 cycles. The treatment with UFT and Leucovorin continued until progression or major toxicity. Response was evaluated after two courses and at every second course during the following treatment. Patients with complete response had an additional three courses of UFT and Leucovorin. Toxicity was evaluated before each treatment course according to WHO criteria.

Table 1

Patient characteristics

Patient characteristics	No. of patients
No. included	97
Gender:	
Males	62
Females	34
Age median (years):	62
(range)	(24–84)
Haemoglobin, mmol/l at start of treatment (mean) (range)	7.8 (5.2–10.3)
Previous adjuvant chemotherapy	9
Location of metastases:	
Liver	71
Lungs	9
Lymph node	3
Other	14
Performance status:	
0	40
1	48
2	9

STATISTICS

Simon's two-stage method was used to calculate the number of patients needed in the trial. The response rate with UFT and Leucovorin alone was estimated at 20%. The target response rate with UFT and Leucovorin combined with mitomycin C was 35%. With a risk of type I error of 5% and a power of 90% the first step was calculated to include 42 patients and cessation of study if the results showed ≤ 8 responders. A number > 8 responders would signal that the study should include 77 patients. The study accrued 97 patients to ensure that 77 were evaluable for response.

RESULTS

A total of 373 courses were administered. The median number of cycles was 4 (range 1–7). Eighty-two patients received at least 2 cycles. Fourteen patients did not complete the treatment due to adverse events or toxicity. Three patients died while under study. Fifty-seven patients stopped treatment owing to progression and the remaining 23 patients were either withdrawn at their own request or on a physician's decision. Table 2 shows reasons for withdrawal.

Table 2

Reason for withdrawal ($n = 97$)

Reason for withdrawal	No.
Adverse event	2
Completed treatment	1
Death	3
Disease progression	57
Other	2
Patient request	9
Physician decision	11
Study drug toxicity	12
Total	97

Eighty-one patients were evaluable for response. Two patients had a complete response and 20 had a partial response. Thus the overall response rate by intention to treat was 23% (15–32%, 95% confidence limits). Forty patients (41%) obtained stabilization and 19 patients (19%) progressed.

The treatment was well tolerated. No toxic deaths were recorded. Twelve patients had dose reduction. Table 3 shows major toxicity. Severe (grade 3/4) toxicity was only seen in a small fraction of the patients, 3 patients experienced anorexia, 6 patients nausea. Vomiting and fatigue were seen in 7 patients and 9 patients respectively. Only 1 patient experienced a febrile sepsis and 1 patient grade 4 neutropenia. There was an insignificant tendency to increased thrombocytopenia during the first 4 courses, but only 1 patient experienced grade 3 thrombocytopenia and 1 patient grade 4 thrombocytopenia. No episodes of haemolytic uraemic syndrome were recorded.

Time to progression is shown in Fig. 1. The median progression free survival was 5 months. It also appears that approximately 15% of the patients were progression free after 12 months.

The crude survival is also shown in Fig. 1. The median survival was 13 months with 35% being alive after 15 months.

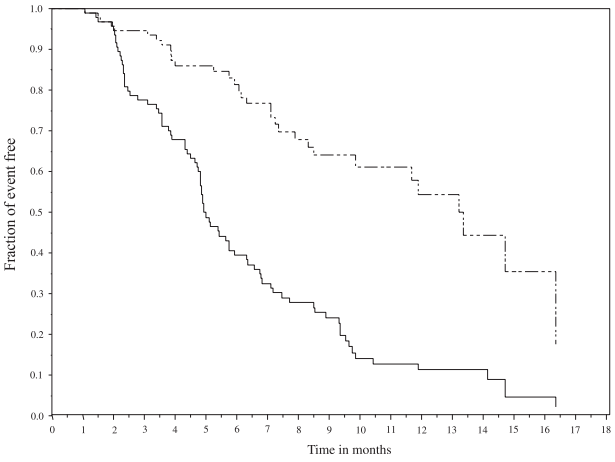

Fig. 1. The upper Kaplan-Meier plot (__..__..) shows the overall survival. The lower curve (_____) shows time to progression.

DISCUSSION

Mitomycin C has been combined with 5-fluorouracil in a number of different settings. The combination seems to improve the effect of radiotherapy. This has clearly been proved in a randomized trial including 585 patients with anal cancer (13) and it may also apply to patients with fixed rectal tumours (14). It is not clear whether the improvement in combination with radiotherapy can be explained by increased radiosensitivity or is due to the cytostatic effect per se.

Table 3

Toxicity (n = 97)

Toxicity	Grade 1–2	Grade 3–4
Anorexia	47	3
Nausea	54	6
Vomiting	36	7
Diarrhoea	32	7
Fatigue	62	9
Bone pain	14	1
Dehydration	1	1
Dyspnoea	2	1
Elevated INR	0	1
Febrile neutropenic sepsis	0	1
Hypercalcaemia	0	1
Hyponatraemia	0	1
Neutropenia	0	1
Renal failure	0	1
Thrombocytopenia	0	2

The combination also appears superior to 5-fluorouracil alone in the treatment of metastatic disease. The study by Ross et al. (12) compared prolonged i.v. infusion of 5-fluorouracil alone with prolonged i.v. infusion of 5-fluorouracil and mitomycin C in a phase III trial including 200 patients. The response rates were 38% and 54%, respectively ($p = 0.02$). The study also showed a significant difference in progression free survival ($p = 0.03$) but not in overall survival. After the first 106 randomized patients 2 episodes of haemolytic uraemic syndrome were recorded. The dose of mitomycin C was reduced from 10 mg/m^2 to 7 mg/m^2 and in the following 89 randomized patients no further haemolytic uraemic syndrome appeared. The response rate dropped insignificantly from 61% to 45%. However, the dose reduction has been claimed to invalidate the conclusion (15). It should be noted that the response rate with 5-fluorouracil alone was remarkably high. However, different response rates may well be explained by different selection criteria. The selection is a major predictor of response, but it does not explain the difference between the two arms. The prolonged i.v. infusion may be important to the effect, as prolonged i.v. infusion (16) seems more effective than bolus 5-fluorouracil.

The combination of UFT and mitomycin C seems an obvious choice as UFT to a certain extent simulates prolonged i.v. infusion of 5-fluorouracil. Furthermore, when mitomycin C is used as in the study, it is an oral regime except for 4 i.v. injections.

Our study did not confirm the high response rate reported in the English trial with prolonged i.v. infusion of 5-fluorouracil and mitomycin C. Nor could we confirm the results of a Japanese phase II trial, which claimed a response rate of 38.5% with UFT and mitomycin C. This trial, however, only evaluated 21 patients and the results should be treated with caution (17).

Toxicity of the present regimen was very low. No cases of haemolytic uraemic syndrome were observed. This is in agreement with Ross et al. Contrary to their results we did not see any plantar–palmar erythema. The frequency of severe bone marrow toxicity was also low in the present study and the same applies to other major side effects. The relative high frequency of fatigue is probably caused more by the disease than the treatment.

In conclusion, the present study aimed to investigate the response rate of UFT and Leucovorin combined with mitomycin C with the intention to confirm the optimistic results obtained with prolonged i.v. infusion of 5-fluorouracil and mitomycin C. The effect described with a response rate of 23% and a time to progression of 5 months is very similar to results seen with 5-fluorouracil and Lecovorin or UFT and Leucovorin alone. The results do not encourage a phase III trial of the present combination.

REFERENCES

1. Borner MM, Schöffski P, de Wit R, et al. Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and Leucovorin: a randomised crossover trial in advanced colorectal cancer. Eur J Cancer 2002; 38: 349–58.
2. Pazdur R, Douilard J-Y, Sillings JR, et al. Multicenter phase II study of 5-fluorouracil (5-fluorouracil) or UFT in combination with Leucovorin (LV) in patients with metastatic colorectal cancer. ASCO 1999; 18: Abstract 1009.
3. Carmichael J, Popiela T, Radstone D, et al. Randomized comparative study of ORZEL (oral uracil tegafur (UFT)) plus Leucovorin (LV) versus parenteral 5-fluorouracil (5-fluorouracil) plus LV in patients with metastatic colorectal cancer. ASCO 1999; 18: Abstract 1015.
4. Hill M, Mackay H, Cunningham D, et al. Phase I/II study of oral uracil/tegafur (UFT®) Leucovorin and irinotecan in patients with advanced colorectal cancer. Ann Oncol 2002; 11 (suppl. 4): Abstract 193P.
5. Javier Dorta F, Feliu J, Vincent J, et al. Phase II clinical trial with the combination of oxaliplatin-UFT-l,-Leucovorin (OXA-UFT-l,LV) for the first line treatment of advanced colorectal cancer (ACC). Preliminary results (Oncopaz Cooperative Group—Spain). Ann Oncol 2002; 11(Suppl. 4): Abstract 220P.
6. Jakobsen A, Pfeiffer P, Hansen F, et al. dual modulation of UFT with Leucovorin and hydroxurea in metastatic colorectal cancer. Acta Oncologica 2001; 40: 63–6.
7. Moore GE, Bross ID, Ausman R, et al. Effects of mitomycin C (NSC-26980) in 346 patients with advanced cancer. Cancer Chemother Rep 1968; 52: 675–84.
8. Moertel C, Reitmeier R, Hahn R. Mitomycin C therapy in advanced gastrointestinal cancer. JAMA 1968; 204: 1045–8.
9. Rusello O, Romanini A, Civalleri D, et al. Time-dependent interactions between 5-fluorouracil and mitomycin C on a human colon cancer cell line, HCT-8, in vitro. EUR J Cancer Clin Oncol 1989; 25: 571–2.
10. Krauss S, Sonoda T, Solomon A. Treatment of advanced gastrointestinal cancer with 5-fluorouracil and mitomycin C. Cancer 1979; 43: 1598–603.
11. Richards F, Case LD, White DR, et al. Combination chemotherapy (5-fluorouracil, methyl-CCNU, mitomycin C) versus 5-fluorouracil alone for advanced previously untreated colorectal carcinoma. A phase III study of the Piedmont OncologyAssociation. J Clin Oncol 1986; 4: 565–70.
12. Ross P, Norman A, Cunningham D, et al. A prospective randomized trial of protracted venous infusion 5-fluorouracil with or without mitomycin C in advanced colorectal cancer. Ann Oncol 1997; 8: 995–1001.
13. Epidermoid Anal Cancer: Results from the UKCCCR Randomised Trial of Radiotherapy Alone Versus Radiotherapy, 5-Fluorouracil, and mitomycin. Lancet. 1996; 348: 1049–54.
14. Chan AK, Wong AO, Langevin J, et al. Preoperative chemotherapy and pelvic radiation for tethered or fixed rectal cancer: a phase II dose escalation study. Int J Radiat Oncol Biol Phys 2000; 48: 843–56.
15. Herrmann R. 5-fluorouracil and mitomycin C in colorectal cancer: unacceptable conclusion. Ann Oncol 1998; 9(2): 230.
16. Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 1998; 16: 301–8.
17. Ikeda E, Kodaira S, Teramoto T, et al. Optimal dosage of UFT+MMC combination chemotherapy for advanced colorectal cancer—phase I/II study of combination chemotherapy of MMC with 2-week intervals and intermittent UFT administration—Study Group of UFTM Therapy for Advanced colorectal cancer. Gan To Kagaku Ryoho 1998; 23: 1291–8.