Weekly high-dose 5-fluorouracil as 24-h infusion and folinic acid (AIO) plus irinotecan as second- and third-line treatment in patients with colorectal cancer pre-treated with AIO plus oxaliplatin

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Our objective was to evaluate the efficacy and safety of high-dose 5-fluorouracil (5-FU) as a 24-h infusion and folinic acid (FA) (AIO regimen) plus irinotecan (CPT-11) after pre-treatment with AIO plus oxaliplatin (L-OHP) in colorectal carcinoma (CRC). Twenty-six patients with non-resectable distant CRC metastases were analyzed for second- or third-line treatment with AIO plus CPT-11 after pre-treatment with AIO plus L-OHP. On an outpatient basis, the patients received a treatment regimen comprising weekly 80 mg/m^2 CPT-11 in the form of a 1-h i.v. infusion and 500 mg/m^2 FA as a 1- to 2-h i.v. infusion, followed by 2000 mg/m^2 5-FU i.v. administered as a 24-h infusion once weekly. A single treatment cycle comprised six weekly infusions followed by 2 weeks of rest. A total of 26 patients received 344 chemotherapy applications with AIO plus CPT-11. The main symptom of toxicity was diarrhea (NCI-CTC toxicity grade 3+4) occurring in five patients (19%; 95% CI 7–39%). Nausea and vomiting presented in two patients (8%; 95% CI 1–25%). The response rate of 26 patients can be summarized as follows: partial remission: *n*=7 (27%; 95% CI 12–48%); stable disease: *n*=9 (35%; 95% CI 17–56%) and progressive disease: *n*=10 (38%; 95% CI 20–59%). The median progression-free survival (*n*=26) was 5.8 months (range 3–13), the median survival time counted from the treatment start with the AIO plus CPT-11 regimen was 10 months (range 2–24) and counted from the start of first-line treatment (*n*=26) was 23 months (range 10–66). We conclude that the AIO regimen plus CPT-11 is practicable in an outpatient setting and well tolerated by the patients. Tumor control was achieved in 62% of the patients. The median survival time was 10 months and the median survival time from the start of first-line treatment (*n*=26) was 23 months. *Anti-Cancer Drugs* 14:745–749 © 2003 Lippincott Williams & Wilkins.

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Introduction

In western countries, colorectal carcinoma (CRC) is one of the most frequent tumor entities, with 130 000 new cases annually in the US and 50 000 new cases in Germany [1,2]. In 40–50% of all those affected, synchronous or metachronous distant metastases, most commonly not resectable, were found and required chemotherapeutic treatment [3,4].

Therapy sequences are of increasing importance in terms of judging the efficacy of palliative treatment of CRC. In a randomized phase III trial, Tournigand *et al.* have shown that median survival times of up to 21 months could be achieved in both therapy groups by applying the FOLFIRI plus FOLFOX versus the FOLFOX plus FOLFIRI therapy sequence [5]. Additionally, recent publications have mainly focused on the efficacy of therapy sequences such as the Saltz regimen plus FOLFOX4, the high-dose 5-fluorouracil (5-FU) as 24-h infusion and folinic acid (AIO) regimen, and the AIO regimen plus irinotecan (CPT-11) sequence, as well as the AIO regimen, and the AIO regimen plus oxaliplatin (L-OHP) sequence [6–8]. To date, only a small number of publications have centered on the value of palliative third-line therapy [9,10].

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In the following, we will report on the efficacy of the AIO regimen plus CPT-11 in patients pre-treated with AIO plus L-OHP in palliative second- and third-line treatment of CRC.

Patients and methods

Patients

This retrospective analysis included only patients with histologically confirmed CRC. The patients revealed distant metastases measuring at least 2 cm in diameter and were definitively not curatively resectable.

Inclusion criteria were an ECOG index $\leqslant 2$, age 18–75 years, adequate bone marrow function, leucocytes $\geqslant 3500/\mu l$, platelets $\geqslant 100\ 000/\mu l$, adequate liver function (serum bilirubin at least $\leqslant 2 \times$ the upper reference range) and renal function (creatinine $\leqslant 1.5 \times$ the upper reference range). All patients had been pre-treated with the AIO regimen plus L-OHP (bi-weekly 85 mg/m^2 i.v.) as palliative first- and second-line treatment. If the AIO regimen plus L-OHP was applied in second-line treatment ($n = 13$), the patients had already received the AIO regimen within the framework of first-line treatment. In eight of 13 patients, who were treated with AIO plus L-OHP in first-line treatment, a curative resection (R0) was first of all performed [11], and in case of recurrence, a second-line treatment with AIO plus CPT-11 was applied. Exclusion criteria were clinically relevant cardiac disease, CNS metastasis or other malignancy underlying disease capable of reducing life expectancy, with the exception of cutaneous basal cell carcinoma and intraepithelial carcinoma of the cervix.

Before initiating treatment, a medical history, physical examination, laboratory investigations, a chest X-ray, a computed tomography (CT) scan of the abdomen and, where relevant complaints presented, further imaging procedures such as a bone scan or a CT scan of the head were obtained. If the tumor burden was confined mainly within the chest, a CT of the thorax was carried out to check the progress of the disease.

Treatment protocol

Prior to treatment, a Port catheter was surgically implanted via the cephalic vein. As palliative second- or third-line treatment, the patients received in outpatient care weekly 80 mg/m^2 CPT-11 (Campto) as a 1-h infusion and 500 mg/m^2 folinic acid (FA; Rescuvolin) as a 1- to 2-h infusion i.v. followed by 2000 mg/m^2 5-FU i.v. administered as a 24-h infusion once weekly applied via a miniature pump system (Intermate LV 5 Baxter). One cycle comprised six weekly infusions followed by 2 weeks of rest. As prophylactic antiemetic, tropisetron (Navoban) 5 mg i.v. and 0.5 mg Atropin were applied s.c. prior to initiating treatment. Treatment was continued up to tumor progression or occurrence of unacceptable toxicity (see Methods).

Prior to each weekly application, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) toxicity was determined and the blood count checked. If during the course of treatment nausea or vomiting of CTC toxicity grade 2 or above occurred, antiemetic treatment was intensified by applying 8 mg of dexamethasone (Fortecortin) i.v. In the event of a CTC grade 2 hand/foot syndrome developing, treatment with vitamin B_6 (Hexobion) 2×100 mg p.o./day was applied. If diarrhea CTC grade 2 or above developed, the patient was instructed to take 4 mg of loperamide (Imodium) p.o. initially and subsequently 2 mg every 2 h for a time period of up to 12 h after the last bowel movement; however, for no longer than 48 h. Immediately after the first bowel movement, the patient should drink a large amount of liquid with electrolytes. If fever occurred due to diarrhea or leukocytopenia (NCI-CTC toxicity grade 3/4), a broad-spectrum antibiotic, e.g. ciprofloxacin (Ciprobay), was given. After every cycle, a follow-up examination comprising a blood count, a serum test for CEA and CA 19-9, an abdominal CT scan, and a chest X-ray was performed.

Methods

The treatment response was checked for all CT images by an experienced radiologist. CT was repeated every 8 weeks or earlier, if clinical deterioration was observed. Antitumor activity was evaluated in accordance with WHO criteria [12].

A carcinoma was defined as resistant to AIO plus L-OHP if imaging techniques confirmed progressive disease (PD) during the course of treatment and the treatment plan had to be switched to palliative treatment with AIO plus irinotecan within 4 weeks.

A carcinoma was defined as refractory to AIO plus L-OHP, if treatment was discontinued without evidence of PD (e.g. by patient request) and if PD was evident after a treatment-free interval of more than 4 weeks, in which case the therapy had to be switched to the AIO plus irinotecan treatment.

Treatment toxicity was evaluated in accordance with the NCI-CTC. If prior to chemotherapy a NCI-CTC toxicity grade 2 was present, treatment was delayed by 1 week (exception: alopecia) or more until a toxicity grade 1 or below was achieved. If a NCI-CTC grade 3 or 4 toxicity presented during the treatment-free interval, the 5-FU and CPT-11 doses for the next applications were reduced to 75% of the planned dose. If toxicity grade 3 or 4 presented again, the dose had to be reduced to 50% for 5-FU and CPT-11. In the event of CTC grade 4 toxicity, an individual decision was taken to terminate treatment.

Statistical considerations

The primary endpoint of the monocentric phase II study was the median survival time after the start of the AIO plus CPT-11 treatment. Secondary endpoints were the rate of tumor control [complete remission (CR) + partial remission (PR) + stable disease (SD)], the progression-free survival (PFS) and the NCI-CTC toxicity grade. Furthermore, the median survival time after the start of first-line treatment was evaluated.

The recruitment was started in January 1999 and terminated in May 2002. The date of analysis was 30 April 2003. By then, all patients, apart from four, had died due to CRC. The Kaplan–Meier method was used to calculate the observed survival. Survival was computed from the start of the AIO plus CPT-11 treatment and from the start of first-line therapy to death from whatever cause. The 95% confidence interval (95% CI) was calculated in accordance with Greenwood [13]. The 95% CIs were computed for clinical response rates and toxicity. All analyses were performed using the statistics software SPSS for Windows Version 10 (SPSS, Chicago, IL).

Results

Twenty-six patients received the AIO regimen plus CPT-11 after pre-treatment with AIO plus L-OHP in palliative second- or third-line treatment after evidence of PD. The median follow-up was 23 months (range 10–66). Additional patient data are depicted in Table 1.

Toxicity and drug administration of AIO plus CPT-11

The symptoms of toxicity experienced by the 26 patients are listed in Table 2. Therapy-related gastrointestinal side effects, in particular higher-grade diarrhea (CTC grade 3), predominated and were seen in five patients (19%; 95% CI 7–39%). Nausea (CTC grade 3) and vomiting (CTC grade 3) occurred in two patients (8%; 95% CI 1–25%). Overall, a total of 344 applications of 5-FU and CPT-11 were given, whereby 220 applications were applied if the AIO plus CPT-11 regimen was chosen for second-line treatment ($n = 13$) and 124 applications if AIO plus CPT-11 was applied for third-line treatment ($n = 13$). In seven of 26 patients (27%), a 5-FU dose reduction proved to be necessary, whereas the 5-FU dose had to be reduced by 25% in all cases. In 10 of 26 patients (38%), the CPT-11 dose had to be reduced, in nine patients by 25% and in one patient by 50%. In three cases, the treatment was terminated due to severe diarrhea (CTC grade 3) by patient request without evidence of PD.

Table 1 Patient characteristics ($n = 26$)

Age (range)	58 (35–75)
Sex (female/male)	6 (23%)/20 (77%)
ECOG status (0/1/2)	10 (38%)/15 (58%)/1 (4%)
Site (colon/rectum)	14 (54%)/12 (46%)
Metastasis (synchronous/metachronous)	19 (73%)/7 (27%)
Metastatic liver surgery (yes/no)	12 (46%)/14 (54%)
Main metastatic lesions (liver/lung/other)	21 (81%)/4 (15%)/1 (4%)
Adjuvant pre-treatment [RT-CT/5-FU/FA (bolus)]	3 (12%)/2 (8%)
AIO plus L-OHP (resistant/refractory)	18 (69%)/8 (31%)

Table 2 Maximum toxicity per patient ($n = 26$) [*n* (%)]

	NCI-CTC grade				
	0	1	2	3	4
Anemia	22 (85)	4 (15)	–	–	–
Leukocytopenia	17 (66)	5 (19)	4 (15)	–	–
Thrombocytopenia	23 (88)	1 (4)	2 (8)	–	–
Nausea	9 (35)	12 (46)	3 (11)	2 (8)	
Vomiting	14 (54)	7 (27)	3 (11)	2 (8)	–
Stomatitis	22 (85)	4 (15)	–	–	–
Limp pain	21 (80)	2 (8)	2 (8)	1 (4)	–
Diarrhea	9 (35)	9 (35)	3 (11)	5 (19)	–
Constipation	24 (92)	2 (8)	–	–	–
Hand–foot syndrome	22 (85)	3 (11)	1 (4)	–	–
Alopecia	25 (96)	1 (4)	–	–	–
Fever	23 (88)	2 (8)	1 (4)	–	–
Eyes (conjunctivitis)	24 (92)	2 (8)	–	–	–
Peripheral sensory neuropathy	25 (96)	1 (4)	–	–	–
Abdominal pain	21 (81)	5 (19)	–	–	–

Clinical response, PFS and median survival of AIO plus CPT-11

Twenty-six patients were evaluable for clinical response to the AIO plus CPT-11 regimen and presented the following results: PR: $n = 7$ (27%; 95% CI 12–48%), SD: $n = 9$ (35%; 95% CI 17–56%) and PD: $n = 10$ (38%; 95% CI 20–59%). The tumor control rate was 62%. The median PFS ($n = 26$) amounted to 5.8 months (range 3–13) and the median survival time counted from the start of the AIO plus CPT-11 treatment was 10 months (range 2–24) (see Fig. 1). If AIO plus CPT-11 was applied for second-line treatment ($n = 13$), the response rate was as follows: PR: $n = 5$ (38%; 95% CI 14–68%), SD: $n = 4$ (31%; 95% CI 9–61%) and PD: $n = 4$ (31%; 95% CI 9–61%). The median PFS amounted to 7.4 months (range 3–13) and the median survival rate to 16 months (range 3–24). If AIO plus CPT-11 was applied for third-line treatment ($n = 13$), the response was PR: $n = 2$ (15%; 95% CI 2–45%), SD: $n = 5$ (38%; 95% CI 14–68%) and PD: $n = 6$ (47%; 95% CI 19–75%). The median PFS amounted to 3.9 months (range 3–6) and the median survival rate to 7 months (range 2–18).

Median survival after the start of first-line therapy

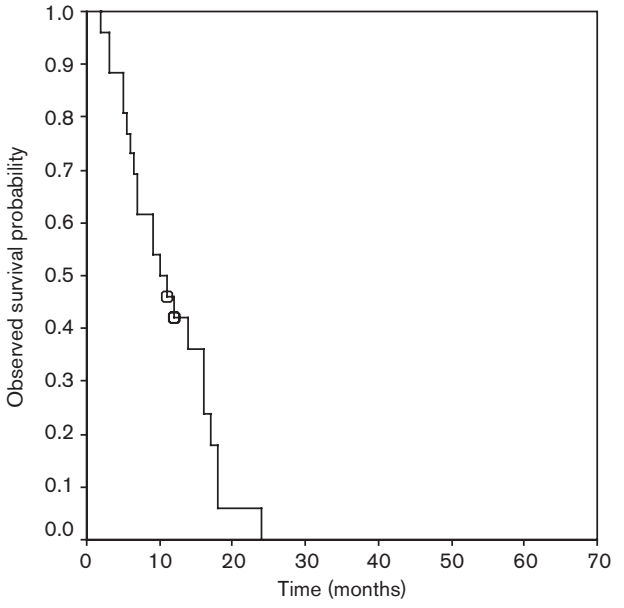
The median survival time counted from the start of first-line treatment was 23 months (range 10–66) (see Fig. 2). With the AIO, AIO plus L-OHP and AIO plus CPT-11 therapy sequence ($n = 13$), the median survival time amounted to 21 months (range 15–66), whereas it was 32 months (range 10–59) for the AIO plus L-OHP and AIO plus CPT-11 ($n = 13$) sequence.

By the date of analysis (30 April 2003), 22 of the 26 patients had died due to the progressive course of their CRC.

Discussion

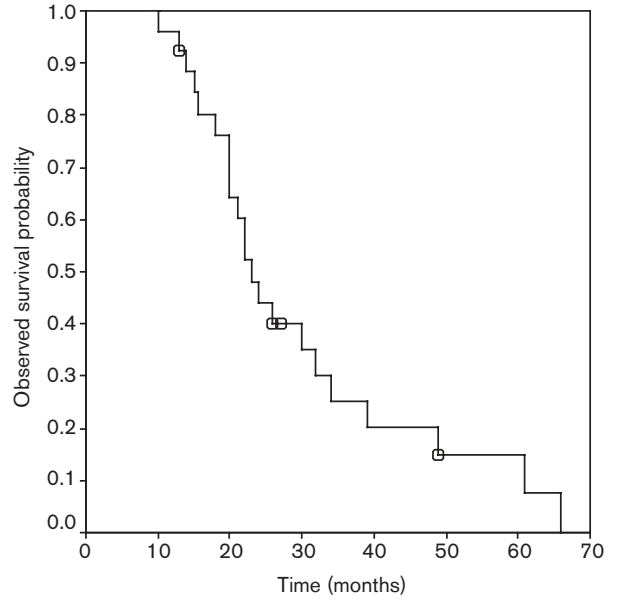
Since CPT-11 and L-OHP drugs have gained access to CRC therapy, the efficacy of palliative treatment for this

Fig. 1



Kaplan–Meier curve after start of AIO plus CPT-11 treatment ($n=26$). Median survival time: 10 months (range 2–24). Circles indicate censored data.

Fig. 2



Kaplan–Meier curve for overall survival after start of first-line therapy ($n=26$). Median survival time: 23 months (range 10–66). Circles indicate censored data.

tumor entity has considerably improved. In prospective studies median survival times of 21 months have been achieved by means of palliative first- and second-line treatment with FOLFIRI/FOLFOX and FOLFOX/FOLFIRI, respectively [5]. The AIO regimen plus CPT-11 is a commonly used treatment schedule applied for palliative first- [14] and second-line treatment of CRC [7]. However, to date, no information is available concerning the efficacy and toxicity of the AIO regimen plus CPT-11 in patients pre-treated with AIO plus L-OHP in palliative first- and second-line CRC treatment.

The AIO regimen plus CPT-11 led to higher-grade diarrhea (CTC grade 3 + 4) in 17.3% and higher-grade leukocytopenia (CTC grade 3 + 4) in 8.6% of the patients [14]. With respect to palliative second-line treatment in the framework of a phase II study, Hofheinz *et al.* reported higher-grade diarrhea (CTC grade 3) in 12%, higher-grade leucopenia (CTC grade 3) in 3% and vomiting (CTC grade 3) in 6% of the patients [7]. This toxicity data is comparable with the results of our study (see Table 2).

By applying the AIO regimen plus CPT-11 after pre-treatment with the AIO regimen, Hofheinz *et al.* could achieve a response rate (PR) of 17%, a tumor control of 57% and a median survival time of 8.4 months in second-line treatment (7). In our study, AIO plus CPT-11 led to a response rate (PR) of 27%, a tumor control of 62% and a median survival of 10 months in patients pre-treated with the AIO regimen plus L-OHP.

The patients ($n = 13$) who had received the AIO regimen plus CPT-11 for second-line treatment after pre-treatment with the AIO regimen plus L-OHP showed a higher tumor control rate (CR + PR + SD) (69 versus 53%) and a longer median survival time (16 versus 7 months, $p = 0.054$) than those patients ($n = 13$) who had obtained the AIO regimen plus CPT-11 for third-line treatment.

One major reason for these results might be the fact that only five of the 13 patients (38%) who had received AIO plus CPT-11 for second-line treatment revealed L-OHP-resistant metastases, while all patients (100%) treated with AIO plus CPT-11 in third-line treatment were L-OHP-resistant.

With regard to palliative third-line treatment based on defined therapy sequences, available information is very limited.

Kallen *et al.* achieved a response rate of 30%, a tumor control of 75% and a median survival time of 13.7 months in 12 patients with third-line treatment in accordance with the AIO regimen plus L-OHP after pre-treatment with the Mayo regimen and the AIO regimen [9].

In a retrospective analysis of the French GERCOR study group, 93 patients obtained a response rate of 5% and a tumor control of 36% with a third-line treatment based on

the de Gramont regimen plus CPT-11 after pre-treatment with the de Gramont regimen and the de Gramont regimen plus L-OHP (10). The median survival time after application of all three treatment regimens was 26 months.

These results are comparable with our data obtained from the subgroup treated with the AIO, AIO plus L-OHP and AIO plus CPT-11 therapy sequence ($n = 13$). In this patient group, a response rate of 15% and a tumor control of 53% were achieved with AIO plus CPT-11. The median survival time after application of all three treatment regimens was 21 months.

In accordance with the Tournigand *et al.* approach, we are currently analyzing the AIO plus CPT-11 treatment sequence after pre-treatment with AIO plus L-OHP in palliative first- and second-line treatment of CRC in a large patient group within the framework of a multicenter phase II study.

The value of palliative third-line treatment remains to be analyzed more intensively in further clinical trials.

Summing up our results, we have shown that the AIO regimen plus weekly CPT-11 offers good tolerability and satisfying efficacy leading to a tumor control of 62% and a median survival time of 10 months after pre-treatment of AIO plus L-OHP. The median survival time counted from the start of first-line treatment amounted to a promising period of 23 months.

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