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Palliative Second-line Treatment with Weekly High-dose 5-Fluorouracil as 24-hour Infusion and Folinic Acid (AIO) plus Oxaliplatin after Pre-treatment with the AIO-Regimen in Colorectal Cancer (CRC)*

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Abstract. *Background and Aims: The aim of this work was to evaluate the efficacy and safety of second-line treatment with weekly high-dose 5-Fluorouracil (5-FU) as a 24-hour infusion (24-h inf.) and folinic acid (FA) (AIO-regimen) plus Oxaliplatin (L-OHP) after pre-treatment with the AIO regimen, focusing in particular on the efficacy of palliative first- and second-line treatment in colorectal carcinoma (CRC). Patients and Methods: Patients with non-resectable distant CRC metastases were enrolled in a prospective phase II study for palliative second-line treatment after previous palliative first-line treatment in accordance with the AIO regimen. On an outpatient basis, the patients received a treatment regimen comprising biweekly 85 mg/m^2 L-OHP in the form of a 2-hour intravenous (i.v.) infusion and 500 mg/m^2 FA as a 1 to 2-hour i.v. infusion, followed by 2,600 mg/m^2 5-FU administered as a 24-h inf. i.v. once weekly. A single treatment cycle comprised 6 weekly infusions followed by 2 weeks of rest. Results: During second-line treatment, a total of 26 patients received 340 chemotherapy applications. As the main symptom of toxicity, diarrhoea (NCI-CTC toxicity grade 3+4) presented in 5 patients (19%; 95% CI: 4-34), followed by nausea (CTC grade 3) in one patient (4%; 95% CI: 0-11). Twenty-three patients were evaluable for treatment response. The remission data can be summarised as follows: Complete remission (CR): n=1 (4%; 95% CI: 0-13); partial remission (PR): n=3 (13%; 95% CI: 0-27); stable disease (SD): n=11 (48%; 95% CI: 27-68) and progressive disease (PD): n=8 (35%; 95% CI: 15-54). The median progression-free survival (PFS) rate (n=26) was 3.3 months (range 0-11.5), the median survival time counted from the start of second-line treatment (n=26) 11.6 months (range 2.1-33.0) and the median survival time counted from the start of first-line treatment (n=26) 19.9 months (range 7.7-49.8). Conclusion: Palliative second-line treatment according to the AIO regimen plus L-OHP is feasible in an outpatient setting and well tolerated by the patients. Tumour control (CR + PR + SD) was achieved in 65% of the patients, the median survival time being 11.6 months. The AIO regimen followed by the 'AIO regimen plus L-OHP' therapy sequence led to a promising median survival time of 19.9 months (range 7.7-49.8).*

In western countries colorectal carcinoma (CRC) is one of the most common tumour entities, with 130,000 new cases annually in the USA and 50,000 in Germany (1, 2). In 40-50% of all those affected, synchronous or metachronous distant metastases are found. In the majority of cases they are non-resectable and require palliative chemotherapy (3).

In 1998, Irinotecan monotherapy was established for CRC second-line treatment in patients previously treated with 5-Fluorouracil (5-FU). Within the framework of a phase III study (n=279), a significant improvement of the 1-year survival rate could be achieved by the application of Irinotecan (36.2%) *versus* best supportive care (13.8%) (p=0.0001) (4). In a further phase III study, the patient group which had received an Irinotecan monotherapy achieved a significantly higher survival rate after 12 months (44.8% *versus* 32.4%, p=0.035) and a better progression-free survival (PFS) (p=0.017) than the group treated with

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Abbreviations: GERCOR: Groupe Coopérateur Multidisciplinaire en Oncologie.

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continuous 5-FU regimens ('de Gramont' regimen, 'Lokisch' regimen, AIO regimen) (5). Altogether, the application of 350 mg/m^2 Irinotecan every 3 weeks seemed to present a more favourable toxicity profile in comparison to the application of 125 mg/m^2 of the same agent once weekly (6).

In several phase II trials the French GERCOR study group investigated different dose levels and application modes of 5-FU, folinic acid (FA) ('de Gramont' regimen), and Oxaliplatin (L-OHP) in CRC patients pretreated with 5-FU. The efficacy of this combination could be proven without initiating further prospective randomised phase III trials (7-11). Moreover, the application of Irinotecan combined with 5-FU and FA ('de Gramont' regimen, AIO regimen) was investigated in some recent phase II trials comprising patients pretreated with 5-FU (12,13).

Altogether, the above-mentioned studies were frequently based on different first-line treatment regimens and made no distinction between 5-FU-resistant and 5-FU-refractory carcinoma. Furthermore, some of the enrolled patients received more than solely one treatment regimen. Hence, it seems exceedingly difficult to draw any definite conclusions concerning the value of palliative second-line treatment from those studies.

The first abstract reporting on the results of the 'FOLFIRI followed by FOLFOX *versus* FOLFOX followed by FOLFIRI' therapy sequence was published in 2001. This treatment sequence was applied in a prospective phase III trial comprising 226 randomised patients and achieved a median survival time of more than 21 months in both treatment groups (14).

In our phase II trial we investigated palliative second-line treatment with weekly high-dose 5-FU as a 24-hour infusion (24-h inf.) and FA (AIO-regimen) plus L-OHP after pre-treatment with the AIO regimen, particularly focusing on the efficacy of palliative first- and second-line treatment in metastatic CRC.

Patients and Methods

Patients. The study protocol of our second-line treatment was approved by the local ethics committee and by the Gastroenterological Oncology Study Group (Arbeitsgemeinschaft Gastroenterologische Onkologie, AGO) of the German Society of Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen, DGVS).

Before admission to the study, written informed consent was obtained from every patient. This monocentric phase II study included only patients with histologically confirmed colorectal cancer after pre-treatment with weekly high-dose 5-FU as a 24-h inf. and FA. One patient suffered from progressive metastatic disease after adjuvant treatment with weekly high-dose 5-FU and FA as a 24-h inf. which had been performed within the framework of a phase III study (15). This patient was additionally enrolled in the above-mentioned study. The patients revealed distant metastases measuring at least 2 cm in diameter and were definitively not curatively resectable. Inclusion criteria were an ECOG index ≤ 2, age ≥ 18 and ≤ 75 years, adequate bone marrow function, leukocytes ≥ 3,500/μl, platelets ≥ 100,000/μl, adequate liver function (serum bilirubin ≤ at least 2 x the upper reference range) and renal function (creatinine ≤ 1.5 x the upper reference range). 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 intra-epithelial carcinoma of the cervix.

Before initiating treatment, a medical history, physical examination, laboratory investigations, a chest X-ray, a 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 tumour burden was confined mainly to the chest, a CT of the thorax was carried out to check the progress of the disease.

Treatment protocol. Prior to first-line treatment, a Port-a-Cath was surgically implanted *via* the cephalic vein. For palliative second-line treatment, the patients received in out-patient care 500 mg/m^2 FA (Rescuvolin®) as a 1 to 2-h intravenous infusion (*i.v.*) followed by 2,600 mg/m^2 5-FU *i.v.* administered as a 24-h infusion (24-h inf.) once weekly applied *via* a miniature pump system (Intermate LV 5 Baxter®) and biweekly 85 mg/m^2 L-OHP (Eloxatin®) as a 2-h infusion. The maximum L-OHP dose per application was 150 mg *i.v.* absolute. One cycle comprised 6 weekly infusions followed by 2 weeks of rest. As prophylactic antiemetic, tropisetron (Navoban®) 5 mg *i.v.* was applied prior to initiating treatment. Treatment was continued up to tumour progression or evidence of unacceptable toxicity.

Prior to each weekly application, the NCI-CTC toxicity was determined and the blood count checked. If, during the course of treatment, nausea or vomiting of CTC toxicity grade ≥ 2 occurred, antiemetic treatment was intensified by applying 8 mg of dexamethason (Fortecortin®) *i.v.*. In the event of a CTC grade ≥ 2 hand-and-foot syndrome developing, treatment with vitamin B6 (Hexobion®) 2 x 100 mg per os/day (p.o./d.) was applied. If a peripheral sensory neuropathy of CTC grade ≥ 2 presented, 3 x 100 mg p.o./d. of the liposoluble vitamins B1 and B6 (Milgamma®) could be optionally given. In the event of diarrhoea (CTC grade ≥ 2), the patient was instructed to take 2 mg of loperamide (Imodium®) after every bowel movement, up to 8 x 2 mg p.o./d. If this medication failed to improve the diarrhoea within 24 h, the patient was hospitalised for re-hydration and medication. After every cycle, a follow-up examination comprising a blood count 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. Computed tomography was repeated every eight weeks or earlier if clinical deterioration was observed. Antitumour activity was evaluated in accordance with WHO criteria (16).

A carcinoma was defined as 5-FU-resistant if imaging techniques confirmed progressive metastatic disease during the course of first-line treatment and the treatment plan had to be switched to palliative second-line treatment within 4 weeks.

A carcinoma was defined as 5-FU-refractory if first-line treatment was discontinued without evidence of progressive metastatic

Table I. *Patient characteristics (n=26).*

Age (range)	60 (35-75)
Sex	
female/male	6 (23%) / 20 (77%)
ECOG status	
0/1/2	11 (42%) / 14 (54%) / 1 (4%)
Colon/rectum	15 (58%) / 11 (42%)
Adjuvant treatment (5-FU/FA bolus)	
yes/no	4 (15%) / 22 (85%)
Metastases:	
synchronous/metachronous	18 (69%) / 8 (31%)
Pre-treatment (AIO-regimen)	
adjuvant/palliative	1 (4%) / 25 (96%)
5-FU-resistant/5-FU-refractory	24 (92%) / 2 (8%)
Main metastatic lesions:	
liver	17 (65%)
lung	8 (31%)
lymph nodes	1 (4%)
Involved organs	
1/2/3	12 (46%) / 8 (31%) / 6 (23%)
CEA (> 5 ng/ml)	
yes/no	24 (92%) / 2 (8%)
CA 19-9 (> 37 U/ml)	
yes/no	14 (54%) / 12 (46%)

disease and if progressive disease was evident after a treatment interval of > 4 weeks, in which case therapy had to be switched to palliative second-line treatment.

The treatment toxicity was evaluated in accordance with the National Cancer Institute Common Toxicity Criteria (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 was achieved. In the event of NCI-CTC toxicity grade 3 or 4 during the treatment-free interval, the 5-FU dose for the next applications was reduced to 75% of the planned dose and the L-OHP dose to 100 mg *i.v.* (absolute). If toxicity grade 3 or 4 presented again, the 5-FU dose had to be reduced to 50% and the L-OHP dose to 75 mg *i.v.* absolute. In the event of a CTC grade 4 toxicity, an individual decision was taken to terminate treatment. If paresthesia with functional impairment (CTC grade 3) occurred, treatment was delayed by 1 week or more until a toxicity grade ≤ 1 persisted. The L-OHP dose was reduced to 100 mg *i.v.* absolute. If, despite the reduction in dose, functional disturbances re-appeared (CTC grade 3), L-OHP was further reduced to 50 mg *i.v.* absolute.

Ten patients (38%) received palliative third-line treatment in accordance with the AIO regimen plus weekly Irinotecan (80 mg/m^2). Two of these patients had stable disease (SD) and 8 progressive disease (PD). The results of palliative first-line treatment according to the AIO regimen had been previously published, particularly focusing on 3 phase II studies (17-19).

Statistical considerations. The primary endpoint of the monocentric phase II study was the rate of tumour control (CR + PR + SD). Secondary endpoints were the median survival time, 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.

Since the efficacy of L-OHP combined with 5-FU/FA for second-line treatment has already been proven by clinical studies, we concentrated on enrolling a total number of n=25 patients. The study was started in September 1998. At the date of analysis (December 31, 2002), all patients had died due to colorectal carcinoma. The Kaplan-Meier method was used to calculate the observed survival of both second-line and first- plus second-line treatment. Survival was calculated from the start of palliative first- and second-line treatment to death from whatever cause. The 95% confidence interval (95% CI) was computed in accordance with Greenwood (20). 95% confidence intervals were calculated for clinical response rates and toxicity. All analyses were performed using the statistics software SPSS for Windows Version 10 (SPSS Inc., Chicago, U.S.A.).

Results

Twenty-six patients received palliative first-line treatment in accordance with the AIO regimen, particularly within the framework of 3 phase II studies (17-19). They were enrolled in the phase II study for palliative second-line treatment from September 1998 to January 2001 after evidence of progressive disease. The median follow-up was 32 months (range 23-52). Additional patient data are depicted in Table I.

Toxicity and drug administration of second-line treatment. The symptoms of toxicity experienced by the 26 patients are listed in Table II. Therapy-related gastrointestinal side-effects, in particular severe diarrhoea (CTC grade 3 + 4), predominated and were seen in 5 patients (19%; 95% CI: 4-34). Altogether, 7 patients (27%; 95% CI: 10-44) experienced a higher grade CTC 3 + 4 toxicity, whereas severe peripheral sensory neuropathy did not present. The median overall L-OHP dose per patient was 518 mg/m^2 (176-1588 mg/m^2). Stationary treatment due to higher grade toxicity did not prove necessary, although 3 patients had to be hospitalised as emergency cases due to tumour-related complaints such as paralytic ileus (2x) and covert perforation of rectal recurrence (1x).

Overall, a total number of 340 5-FU applications and 171 L-OHP applications were given and patients received an average of 13 chemotherapy applications each.

Owing to a CTC toxicity grade 2 or higher at the start of treatment, chemotherapy was delayed on 27 occasions (7.9% of the applications) by one (23x) or two (4x) weeks. The

Table II. *Maximum toxicity per patient (n=26) in percentage (%).*

NCI-CTC Grade	0	1	2	3	4
Anemia	19 (73%)	2 (8%)	5 (19%)	---	---
Leukocytopenia	22 (85%)	3 (11%)	1 (4%)	---	---
Thrombocytopenia	24 (92%)	1 (4%)	1 (4%)	---	---
Nausea	10 (38%)	11 (42%)	4 (16%)	1 (4%)	---
Vomiting	21 (81%)	3 (11%)	2 (8%)	---	---
Stomatitis	23 (88%)	1 (4%)	2 (8%)	---	---
Diarrhoea	7 (27%)	7 (27%)	7 (27%)	3 (11%)	2 (8%)
Constipation	24 (92%)	2 (8%)	---	---	---
Hand Foot Syndrome	17 (66%)	5 (19%)	4 (15%)		
Alopecia	21 (81%)	4 (15%)	1 (4%)	---	---
Fever	25 (96%)	1 (4%)	---	---	---
Eyes (Conjunctivitis)	24 (92%)	2 (8%)	---	---	---
Peripheral Sensory Neuropathy	13 (50%)	6 (23%)	7 (27%)	---	---

Table III. *Weekly 24-h infusion of high-dose 5-FU and folinic acid with Oxaliplatin in palliative second-line treatment: different regimens.*

Author	n	Oxaliplatin (2-h *i.v.*)	Folinic Acid (2-h *i.v.*)	5-FU (24-h *i.v.*)
Buechele *et al.* 1999	39	60 mg/m^2 *i.v.* d 1, 8, 15, 22 qd: 36	500 mg/m^2 *i.v.* d 1, 8, 15, 22 qd: 36	2,6 g/m^2 *i.v.* d 1, 8, 15, 22 qd: 36
Bleiberg *et al.* 1999	79	130 mg/m^2 *i.v.* d 1 qd: 21	500 mg/m^2 *i.v.* d 1, 8 qd: 21	2,6 g/m^2 *i.v.* d 1, 8 qd: 21
Van Cutsem *et al.* 1999	57	85 mg/m^2 *i.v.* d 1, 15, 29 qd: 50	500 mg/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 50	2,6 g/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 50
Janinis *et al.* 2000	32	50 mg/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 50	500 mg/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 50	2,5 g/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 50
Present study	26	85 mg/m^2 *i.v.* d 1, 15, 29 qd: 57	500 mg/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 57	2,6 g/m^2 *i.v.* d 1, 8, 15, 22, 29, 36 qd: 57

treatment delays were caused by the following side-effects: 11x diarrhoea, 3x infection of the upper respiratory tract, 3x persisting nausea, 1x anaemia with erythrocyte substitution, 1x severe vomiting and 2x paralytic ileus. On 6 further occasions, treatment was delayed due to personal reasons.

In 9 out of 26 patients (35%; 95% CI: 16-53), a 5-FU dose reduction proved to be necessary. Altogether, the 5-FU dose had to be reduced in 38 out of 340 applications (11%). In 28 applications, a 5-FU dose reduction to 75% was necessary; in a further 10 cases, the 5-FU dose had to be reduced to 50%.

Additionally, in 9 out of 26 patients (35%; 95% CI: 16-53) the L-OHP dose had to be reduced. Altogether, dose modifications were necessary in 37 out of 171 L-OHP applications. Thirty-two applications were given with 100 mg L-OHP *i.v.* absolute, 1 application with 75 mg L-OHP *i.v.* and 2 applications with 50 mg L-OHP *i.v.*. In 2 patients the L-OHP treatment had to be discontinued, in the first case due to severe diarrhoea and in the second owing to allergic reactions (flush).

Clinical response, PFS and median survival time of second-line treatment. Twenty-three patients were evaluable for the clinical response of second-line treatment. The results are as follows: CR: n=1 (4%; 95% CI: 0-13); PR: n=3 (13%; 95% CI: 0-27); SD: n=11 (48%; 95% CI: 27-68); and PD: n=8 (35%; 95% CI: 15-54). Three patients discontinued their treatment before terminating the first cycle. The reasons were: 1x a covert tumour perforation in the rectal area, 1x an ileal stoma repositioning and 1x severe diarrhoea as therapy-related side-effect.

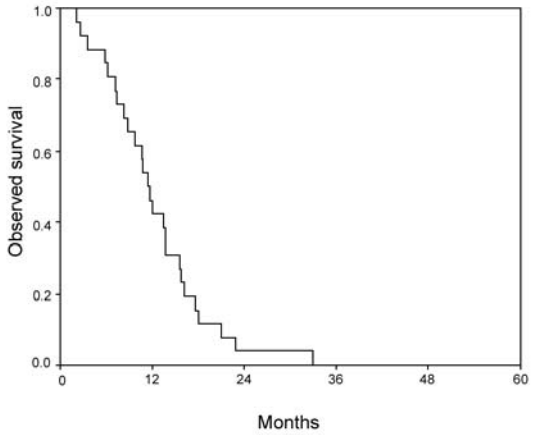

Figure 1. *Kaplan-Meier curve for observed survival with second-line treatment (n=26). Median survival time of second-line treatment: 11.6 months (2.1-33.0).*

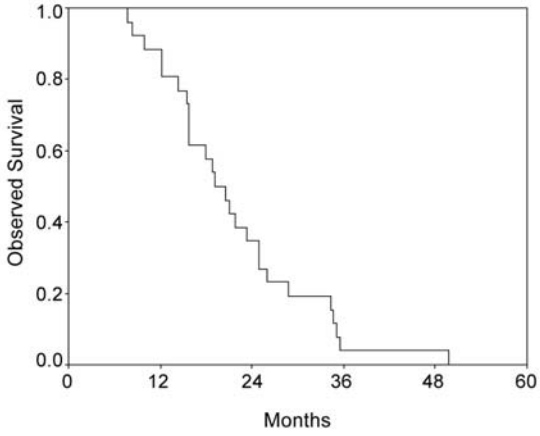

Figure 2. *Kaplan-Meier curve for observed survival with first- and second-line treatment (n=26). Median survival time of first- and second-line treatment: 19.9 months (range 7.7-49.8).*

The median PFS (n=26) was 3.3 months (range: 0-11.5), the median survival time counted from the start of second-line treatment was 11.6 months (range 2.1-33.0) (see Figure 1), and the 1-year survival rate 42%.

Clinical response and PFS of first-line treatment. Twenty-five patients were evaluable for clinical response of first-line treatment, the results being as follows: CR: n=2 (8%; 95% CI: 0-19); PR: n=9 (36%; 95% CI: 17-55); SD: n=11 (44%; 95% CI: 25-63); and PD: n=3 (11%; 95% CI: 0-25). In one patient, the AIO regimen was applied as adjuvant treatment. In the framework of a secondary metastatic resection, a paraaortal lymphadenectomy with adrenalectomy right (R0) was performed in one patient who had been developing both adrenal metastasis and lymph node metastases. In addition, a resection of the inferior lobe of the right lung followed by a curative resection of the inferior lobe of the left lung was performed in a patient with lung metastases and SD (minor response). Both patients later redeveloped distant metastases. The median PFS for the total number of 26 patients was 9.5 months (range: 3.5-29.9 months).

Median survival time of first- and second-line treatment. The median survival time counted from the start of first-line treatment was 19.9 months (range 7.7-49.8) (see Figure 2). By the date of analysis (31.12.2002), all of the 26 patients had died due to the progressive course of their colorectal cancer disease.

Discussion

As yet, no generally accepted standard regimen has been established for palliative second-line treatment with 5-FU, FA and L-OHP in CRC. According to recently published data, FOLFOX4 is the prevalent regimen within the framework of clinical studies (21-23).

In 4 phase II studies investigating CRC second-line treatment, different schedules were chosen for the application of weekly high-dose 5-FU as a 24-h inf. and FA with L-OHP (see Table III). To date, however, the results of 3 of these studies have been published solely as abstracts. Based on our experience in the field of neoadjuvant treatment in primary resectable liver metastases of colorectal cancer, we applied the AIO regimen with bi-weekly 85 mg/m^2 L-OHP (24). In a phase II study in accordance with the AIO regimen plus L-OHP (130 mg/m^2) every three weeks, diarrhoea (NCI-CTC toxicity grade 3) presented in 10%, nausea and vomiting (NCI-CTC grade 3+4) in 7.6% and leukocytopenia (NCI-CTC grade 3+4) in 11.4% (25).

In an alternative phase II study with weekly L-OHP (60 mg/m^2), the following therapy-related side-effects were reported: diarrhoea toxicity grade 3 in 31% and grade 4 in 12%, as well as nausea and vomiting (toxicity grade 3) in 16% (26). A further clinical study equally based on the application of weekly L-OHP (50 mg/m^2) stated as side-effects a toxicity grade 3 diarrhoea in 38% and a grade 4 diarrhoea in 16%, followed by nausea and vomiting (toxicity grade 3+4) in 28% and thrombocytopenia in 13% of the patients. Additionally, 2 therapy-related deaths were reported (27). In comparison with these results, the bi-weekly L-OHP application of 85 mg/m^2 in our study resulted in a lower toxicity rate, the only case of higher grade NCI-CTC toxicity being diarrhoea (grade 3+4) in 19% of the patients (see Table II). Altogether, in none of the studies did any severe neurotoxicity symptom present. Only one study reported on a grade 3 neurotoxicity of 7.6% (28). This moderate neurotoxicity

rate might be explained by the comparatively low L-OHP overall dose per patient in CRC second-line treatment. The mean overall L-OHP dose per patient in our study was 518 mg/m^2.

In the 4 above-mentioned second-line phase II studies, the response rate varied between 7% and 20%; tumour control (CR + PR + SD) could be achieved in 42% to 80% of the patients (25-28). Janinis *et al*. reported on a median survival time of 9 months, whereas in Van Cutsem's abstract a median survival time of 10.1 months was stated. These data are comparable with the results of our study which achieved a response rate of 17%, a tumour control rate of 65% and a median survival time of 11.6 months.

The L-OHP dose intensity seems to play a decisive role in view of the efficacy of second-line treatment (29). Due to the good tolerability in our phase II study, a limitation of the L-OHP dose to a maximum of 150 mg *i.v.* per bi-weekly application does not appear justifiable, whereas it seems strongly recommendable to implement the L-OHP application of bi-weekly 85 mg/m^2 *i.v.* L-OHP in CRC second-line treatment.

The question of therapy sequence is of utmost importance in terms of valuing the efficacy of palliative CRC treatment. Recently, a randomised phase II study compared the FOLFOX4 regimen with the 'de Gramont' regimen plus Irinotecan and the 'L-OHP plus Irinotecan' combination regimen after previous treatment with 5-FU. These regimens did not differ significantly in terms of tumour control, median survival time and quality of life. As expected, the toxicity spectra varied according to the applied regimens (30).

In a phase III study with 821 randomised patients it could be proven that the FOLFOX4 regimen offered a significant improvement of both the response rate and the PFS compared with the L-OHP monotherapy and the 'de Gramont' regimen after pre-treatment with Irinotecan, 5-FU and FA ('Saltz' regimen) (22). Tournigand's phase III study, however, was the first to achieve a median survival of more than 21 months in both treatment groups by the application of the 'FOLFIRI plus FOLFOX *versus* FOLFOX plus FOLFIRI' therapy sequence (14). The present study which was based on the AIO regimen and the 'AIO regimen plus L-OHP' therapy sequence could also achieve a median survival of 19.9 months.

Summing up our results, we have proven that the AIO regimen with bi-weekly 85 mg/m^2 L-OHP offers good tolerability and satisfactory efficacy leading to a tumour control of 65% and a median survival time of 11.6 months. Palliative first- and second-line treatment with weekly high-dose 5-FU as a 24-h inf. and FA (AIO regimen) and the same regimen plus L-OHP in colorectal carcinoma achieved a promising median survival time of 19.9 months.

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