Safety and efficacy of outpatient treatment with CPT-11 plus bolus folinic acid/5-fluorouracil as first-line chemotherapy for metastatic colorectal cancer

Markus Moehler[a], Tanja Hoffmann[a], Christine Zanke[b], Horst Hohl[b], Helmut Burg[c], Peter Ehscheid[d], Peter Schwindt[e], Bernd Adami[f], Martin Schroeder[g], Ortwin Klein[h], Michael Baldus[i], Peter R. Galle[a] and Michael Heike[a]

The combination of irinotecan (CPT-11), bolus 5-fluorouracil (5-FU) and folinic acid (FA) (Saltz regimen) has recently been questioned as first-line chemotherapy for metastatic colorectal cancer after high early death rates due to gastrointestinal and thromboembolic events were reported in two US trials. Therefore, we carefully evaluated the safety and efficacy of this regimen, with high value placed on the management of delayed diarrhea. Forty-six patients with metastatic colorectal cancer received this first-line treatment in nine German outpatient clinics. Dose reductions were mandatory from the first cycle in case of toxicity grade >2. Chemotherapy was administered only to diarrhea-free patients. During a total of 175 cycles administered treatments were delayed for 1 week in 11.6% and given at a reduced dose in 14.5%. All and 40 patients were evaluable for toxicity and response, respectively. Grade 3/4 toxicities included diarrhea ($n=10$), leukopenia ($n=9$), neutropenia ($n=3$) and anemia ($n=4$). One non-fatal pulmonary embolism occurred. Four complete responses (CR) and 10 partial responses were seen, for an overall response rate of 35%. In addition, 16 patients (40%) had stable disease. Resectability of liver metastases was achieved in three patients, including one pathologically confirmed CR. Median progression-free and overall survival were 5 and 13 months, respectively. We conclude that outpatient treatment with the Saltz regimen was well tolerated. Severe gastrointestinal toxicity and thromboembolic events were rarely observed and never fatal. As downstaging was possible, combinations of CPT-11 and FA/5-FU should be further investigated in neoadjuvant protocols. *Anti-Cancer Drugs* 14:79–85 © 2003 Lippincott Williams & Wilkins.

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Outpatient Clinics of the [a]Department of Internal Medicine I, University of Mainz, Mainz, [b]Hospital Bad Ems, Bad Ems, [c]Hospital Simmern, Simmern, [d]Hospital Neuwied, Neuwied, [e]Hospital Andernach, Andernach, [f]General Practice Alzey, Alzey, [g]Hospital St Vincentius, Landau, [h]General Practice Kostheim, Kostheim and [i]General Practice Ruesselsheim, Ruesselsheim, Germany.

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Correspondence to M. Moehler, Department of Internal Medicine I, Johannes Gutenberg University, Langenbeckstrasse 1, 55101 Mainz, Germany.
Tel: +49 6131 177146; fax: +49 6131 173438;
e-mail: moehler@mail.uni-mainz.de

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Introduction

Carcinoma of the colon and rectum is the second most common cause of death from cancer. Although most patients present with surgically resectable disease, almost half will eventually die from metastatic disease [1]. Fluoropyrimidines are the most often used and best investigated drugs for adjuvant and palliative chemotherapy [2,3]. 5-Fluorouracil (5-FU) is usually biomodulated with folinic acid (FA) to increase its affinity for thymidylate synthase [4–6]. Among various 5-FU schedules, the bolus FA/5-FU regimen of [5] is still frequently used as first-line palliative therapy [3], even though recent evidence from clinical studies suggests that combinations of FA/5-FU with the new agents irinotecan or oxaliplatin result in improved response rates and prolonged survival [7–10].

Irinotecan (CPT-11), a potent inhibitor of the enzyme topoisomerase I [11,12], has demonstrated antitumor activity against metastatic colorectal cancer when used alone or in combination as first-line treatment or after failure of FA/5-FU (for review, see [12–14]). In the first-line setting, two randomized multicenter phase III trials demonstrated synergistic activity of CPT-11 with both bolus and infusional FA/5-FU regimens [7,8]. In both studies, the combination of CPT-11 and FA/5-FU was superior to the control arms, CPT-11 alone or FA/5-FU, with regard to response rate, progression-free and overall survival. Recently, however, the combination regimen of CPT-11 and bolus FA/5-FU regimen has attracted criticism after unexpectedly high early death rates (2.5 and 3.5%, respectively) due to gastrointestinal toxicity and thromboembolic events were observed in two subsequent trials [15,16]. Before the onset of the current

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debate, this weekly regimen was widely studied [3,7,12,17] and the latest reanalysis of clinical trials by the Oncology Drug Advisory Committee of the FDA reconfirmed the safety of the regimen: toxicities were found to be comparable to the FA/5-FU control arms [18].

So far no data are available on this CPT-11/bolus FA/5-FU regimen from European countries. Therefore we initiated this prospective open-label, multicenter trial in Germany to evaluate the toxicity and efficacy of this regimen as first-line treatment in patients with metastatic colorectal cancer. We were especially interested in the safety of this regimen in an outpatient setting, with a high emphasis placed on the prompt and aggressive management of delayed diarrhea with loperamide and budesonide, hospitalization and parenteral rehydration in case of refractory diarrhea lasting more than 48 h.

Patients and methods

Patients were recruited consecutively from nine German outpatient clinics (one university hospital, four smaller community hospitals and four General Practices). Eligible patients had histologically documented adenocarcinoma of the colon or rectum and progressive measurable metastatic disease, age 18–75 years, minimum life expectancy of 3 months, Karnofsky performance status $\geq$60, adequate hematological, hepatic and renal function, and no prior chemotherapy for metastatic disease. Any previous adjuvant 5-FU-based therapy with or without radiation therapy had to be completed at least 6 months prior to study entry. Patients with CNS metastases or bowel obstruction or ileus were excluded from the study. The study was approved by the ethics commission board responsible for all participating institutions. Before treatment, all patients gave written informed consent.

As previously described [7], treatment consisted of CPT-11 125 mg/m^2 given as a 90-min i.v. infusion followed by folinic acid 20 mg/m^2 and 5-FU 500 mg/m^2 by i.v. bolus injection administered on days 1, 8, 15 and 22. Treatment was repeated every 6 weeks.

To prevent expected toxicities, patients were carefully informed of the potential risk of delayed diarrhea and neutropenia, and the need for early intervention with loperamide [19] and metoclopramide, prophylactic antibiotics or hospitalization and parenteral rehydration in case of refractory diarrhea lasting more than 48 h. Patients with loperamide-resistant diarrhea defined as loose stools persisting for more than 24 h despite adequate treatment with loperamide received a trial of the oral steroid budesonide (9 mg t.i.d. for a maximum of 4 days) [20]. Atropine was given as needed for irinotecan-related cholinergic symptoms [21]. Antiemetic agents were administered at the discretion of the treating physician. The prophylactic use of colony stimulating factors was not permitted. Treatment was continued until one of the following occurred: disease progression, unacceptable adverse effects or withdrawal of consent by the patient.

Primary end points of the study were the overall objective response rate [ORR = complete (CR) and partial responses (PR)], overall survival and quality of life. Secondary end points included the disease control rate [ORR + stable disease (SD)], progression-free survival, and frequency and severity of toxicities. The quality of life was assessed after inclusion into the study and as often as possible during the course of treatment, using the EORTC-QLQ-C30 (version 2) questionnaire [22].

Safety assessments and complete blood counts were performed weekly. Toxicity was graded according to WHO criteria. In case of any toxicity grade 2 except hand–foot syndrome or alopecia, the next planned doses of irinotecan, folinic acid and 5-FU were delayed for a maximum of 1 week (or resolution of diarrhea for at least 5 days). In case of toxicity grade 3/4 or if improvement from grade 2 to 1 (or resolution of diarrhea) was not reached by 2 weeks, the following chemotherapy doses were reduced by 20%. If grade 3/4 toxicity did not improve by 2 weeks, treatment was discontinued. In contrast to the original study by Saltz *et al.* [7], dose reductions were mandatory from the first cycle of chemotherapy in case of toxicity grade >2 and chemotherapy was resumed only after complete recovery from diarrhea.

Tumor response was assessed according to WHO criteria. Tumor reassessment by the same imaging method used to establish baseline tumor measurement was generally performed after every two courses of therapy until progression. Confirmed objective responses were those for which a follow-up scan obtained at least 4 weeks later demonstrated the persistence of the response. The assessment of response and progression was based on investigator-reported measurements.

Statistical analysis including survival analysis according to Kaplan–Meier was performed with the SPSS software package. The deadline for data evaluation was 1 June 2002. Survival was measured from the time of first administration of chemotherapy to the date of death or last follow-up. Progression-free survival was calculated from treatment onset to the time of progression, study withdrawal or death of any cause. Patients who received at least one dose of the treatment regimen were evaluable for toxicity and patients who completed at least two chemotherapy cycles were evaluable for response.

Results

Between June 2000 and September 2001, 46 consecutive patients with metastatic colorectal cancer were enrolled

into the study. The baseline characteristics of the patients are shown in Table 1. Median age was 62 years (range 43–73). Most patients had a good performance status although more than half of the patients had two or more metastatic sites. All but two patients had previous surgery. Fourteen patients received prior adjuvant chemotherapy with or without radiation therapy. All and 40 patients were evaluable for toxicity and response, respectively.

The patients received a total of 175 chemotherapy cycles (median 4 per patient) including 640 weekly treatments. Overall, 74 (11.6%) of 640 weekly treatments were delayed for 1 week and 93 (14.5%) were given at a reduced dose. The most common cause for discontinuation of study treatment was disease progression or clinical deterioration ($n = 23$). Other reasons included unacceptable toxicity ($n = 4$), tumor response ($n = 5$), death ($n = 3$) and patient refusal ($n = 5$). Three patients were entered later on another clinical trial with an epidermal growth factor receptor antagonist. In one case the reason for withdrawal was unknown. Overall, 25 patients (54%) received at least one additional treatment after discontinuation of the Saltz regimen: 12 patients received oxaliplatin (almost always in combination with FA/5-FU) and the remainder were treated with other chemotherapy regimens and/or radiation ($n = 1$) or surgery ($n = 3$).

Hematological toxicity was mild to moderate in the majority of patients (Table 2). Nine patients (20%) had grade 3/4 leukopenia, three patients (7%) had grade 3 neutropenia and four patients (9%) had grade 3 anemia. Mild thrombocytopenia occurred in one patient. The predominant non-hematological toxicity was delayed diarrhea that reached grade 3/4 in 10 patients (22%) (Table 3). Other non-hematological toxicities were rarely severe (grade 3 nausea and vomiting in four patients, grade 3 acute diarrhea in three patients and grade 3 fever in one patient). Mild to moderate hand–foot syndrome developed in two patients and another patient had a severe exacerbation of psoriasis that was possibly related to 5-FU. Non-fatal pulmonary embolism occurred in one patient, and another patient with pre-existing thrombosis of the iliac arteries and no diarrhea died 12 days after the start of treatment of an unknown cause. There were eight hospital admissions, two of which were treatment-related; both patients had grade 3/4 leukopenia and grade 3 diarrhea, and were admitted for rehydration. Other adverse events with hospitalizations in single patients included a bowel obstruction due to local recurrence, unexplained vertigo and renal failure due to urether obstruction. Regarding the CPT-11 induced delayed diarrhea, 17 patients received at least 1 course (median 2; range 1–5) of loperamide and six patients 1 or 2 courses of budesonide for loperamide refractory diarrhea.

Four CRs and 10 PRs were seen, for an ORR of 35% (Table 4). In addition, 16 patients (40%) had SD (disease control rate, 75%). Disease progression occurred in 10 patients (25%). Resectability of liver metastases was achieved in three patients. Remarkably, one of these patients attained a pathologically confirmed CR (Fig. 1). The two other patients denied the liver resection after discussion with the surgeon. Median progression-free survival was 5 months and overall survival was 13 months

Table 1 Patient characteristics

Characteristics	No.
No. patients	46
Gender (male/female)	23/23
Median age [years (range)]	62 (43–73)
Karnofsky performance status	
90–100	36
70–80	8
60	1
Primary tumor site	
colon	22
rectum	24
Metastatic sites	
liver	34
lung	12
lymph nodes	15
local relapse	4
other sites	7
No. of metastatic sites	
1	20
2	21
≥3	5
Previous treatment	
surgery only	29
surgery + radiotherapy	4
surgery + adjuvant chemotherapy	5
surgery + radiotherapy + adjuvant chemotherapy	6
none	2

Table 2 Hematological toxicity (no. of patients)

	WHO grade			
	1	2	3	4
Leukopenia	9	8	7	2
Neutropenia	4	2	3	–
Anemia	11	5	4	–
Thrombocytopenia	1	–	–	–

Table 3 Non-hematological toxicities (no. of patients)

	WHO grade			
	1	2	3	4
Nausea/vomiting	13	13	4	–
Acute diarrhea	6	3	3	–
Delayed diarrhea	8	7	9	1
Cholinergic syndrome	8	–	–	–
Fever	4	6	1	–
Mucositis	5	–	–	–
Obstipation	6	–	–	–
Asthenia	8	2	–	–

(Fig. 2). At the time of last follow-up, 18 patients were still alive.

Quality of life data were obtained before and at least once during treatment from all patients. The assessment forms of 24 patients were fully completed, allowing us to determine the change from baseline in quality of life during chemotherapy. The 24 patients evaluable for quality of life did not differ in their pattern of response to chemotherapy from the total population of 40 evaluable patients. Global health status improved slightly during treatment compared with pre-therapy values (Fig. 3). In addition, patients treated with the Saltz regimen had a small increase in emotional and physical functioning compared with a previously reported cohort of untreated patients [22]. No remarkable changes in the other items of the questionnaire were seen during treatment, especially with regard to therapy-dependent symptoms nausea and vomiting, diarrhea, pain and fatigue.

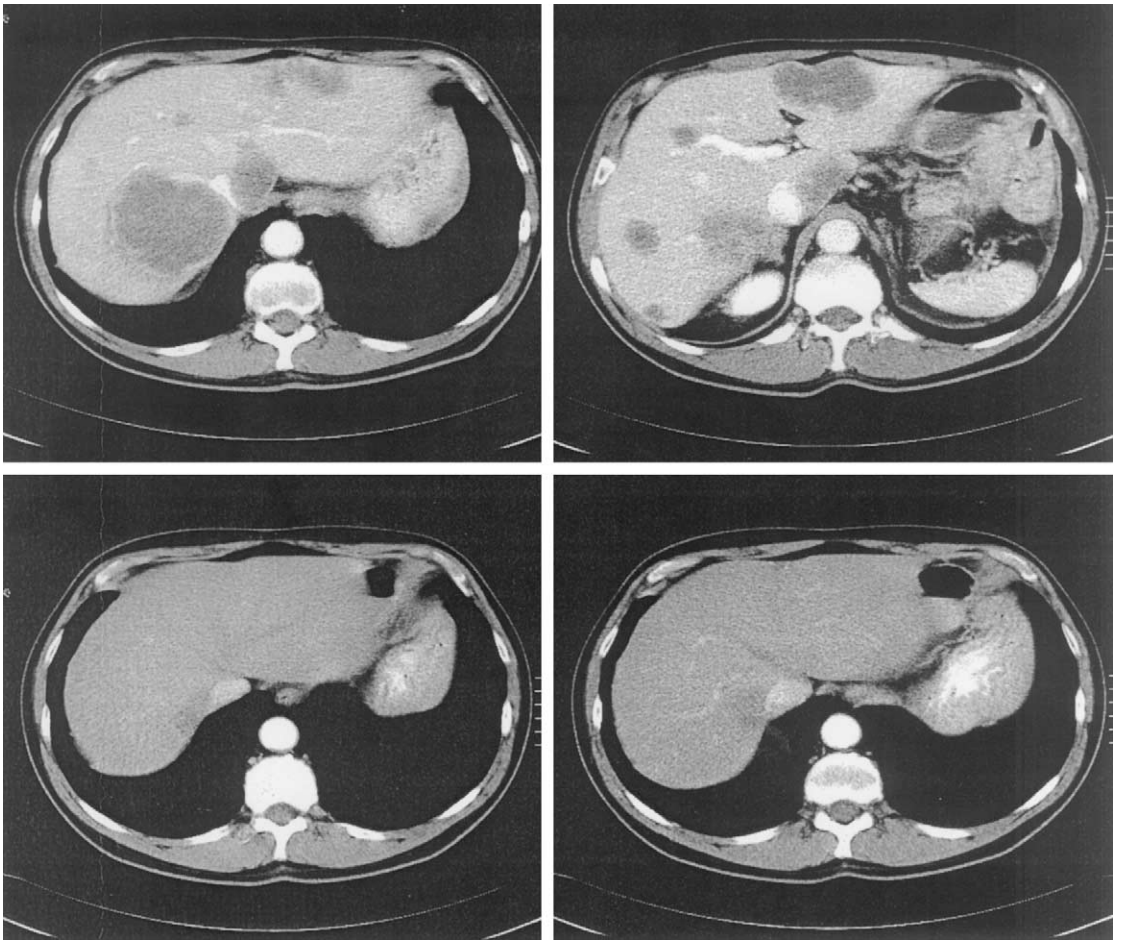
Table 4 **Response (40 evaluable patients)**

	No. (%)
CR	4 (10)
PR	10 (25)
ORR (CR + PR)	14 (35)
SD	16 (40)
Tumor control rate (CR + PR + SD)	30 (75)
Progressive disease	10 (25)

Discussion

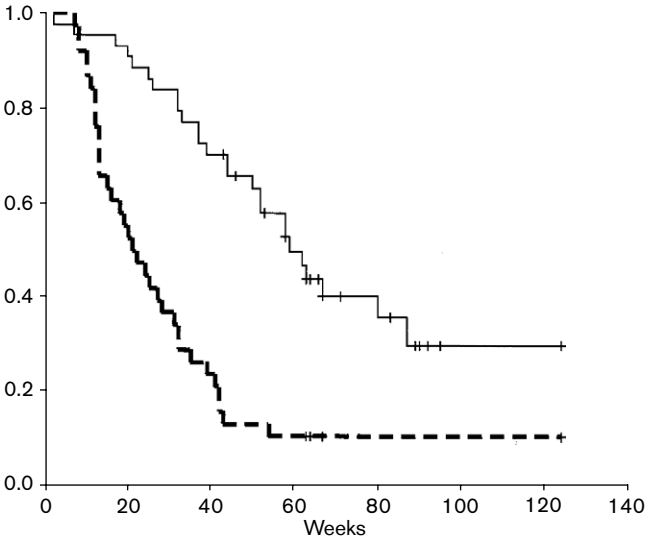
In this study we evaluated the toxicity and efficacy of the combination of CPT-11 with bolus FA/5-FU as first-line chemotherapy for metastatic colorectal cancer. This regimen has been one of the most commonly used chemotherapy protocols for metastatic colorectal cancer in North America since the publications of Saltz *et al.* [7,12,17]. However, after unexpectedly high early death

Fig. 1



Computed tomography (CT) scans of a patient with pathologically confirmed CR. CT scans of a patient with liver metastases who achieved a pathologically confirmed CR. Top row: the patient presented with multiple liver lesions in October 2000. Bottom row: complete disappearance of all lesions after 8 months of treatment with the Saltz regimen.

Fig. 2



Overall and progression-free survival. The overall and progression-free survival (weeks) is depicted as Kaplan–Meier-curves. Overall survival is depicted as a linear line; the progression-free survival as a dotted line.

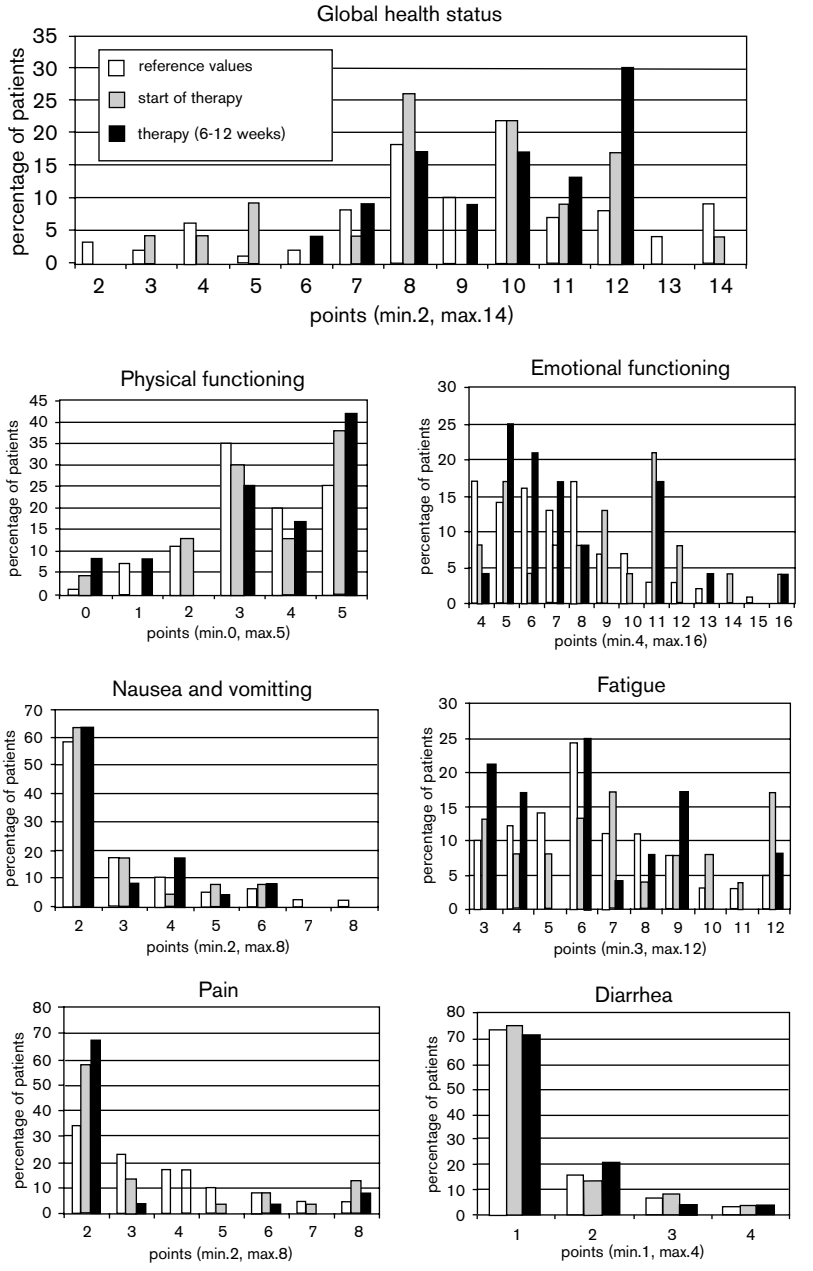
rates due to gastrointestinal toxicity and thromboembolic events were reported in two subsequent trials, the safety of the Saltz regimen has become a subject of considerable debate [15,16]. Based on our experience with this regimen in a community-based outpatient setting we cannot support these safety concerns. Overall, our data are in keeping with the results of the latest reanalysis of clinical trials of the Saltz regimen conducted by the Oncology Drug Advisory Committee of the FDA [18].

In the majority of our patients the regimen was well tolerated. Severe gastrointestinal toxicity and thromboembolic events were rarely observed and never fatal. Most hospitalizations were for prevention rather than treatment of life-threatening conditions. Delayed diarrhea, a well-known side effect of irinotecan [19,20], was generally managed in the outpatient setting using loperamide, which had to be administered to approximately one-third of the patients. Budesonide, which has demonstrated activity in loperamide-refractory diarrhea [20], was required in only 13% of our patients. Moreover, our findings indicate that the Saltz regimen did not affect quality of life. In contrast, we observed improved physical and emotional functioning, and an increase in global health status during treatment. This is in line with the initially reported data that showed no difference in quality of life between the patients treated with the Saltz regimen and those treated with FA/5-FU [7].

The response rate achieved in our study is also consistent with published data [7]. The ORR of 35% is nearly identical with the confirmed response rate of 39% in the initial Saltz study. Tumor control (CR + PR + SD) was achieved in 75% of our patients, which is similar to other reports [7,17]. Median progression-free and overall survival, however, were only 5 and 13 months in our study compared with 7 and 14.8 months, respectively, in the original Saltz study [7]. Three reasons may account for these differences in survival between the studies. (i) The most important reason may be that as much as 37% of our patients had previously received adjuvant FA/5-FU-containing chemotherapy or radiotherapy compared with only 14% of the patients in the initial US study. (ii) Our study included more patients with carcinoma of the rectum (52 versus 16%). (iii) A higher percentage of patients in our study had two or more metastatic sites, indicating a larger tumor burden and consequently worse prognosis regarding survival [7].

It appears particularly noteworthy that after chemotherapy three of our patients achieved surgical resectability of their metastases. To our knowledge these results are the first ever reported to suggest a potential role for the Saltz regimen in the neoadjuvant setting. So far, mainly studies of regional chemotherapy for initially unresectable colorectal liver metastases could demonstrate some success with secondary curative surgery [23,24]. In two recently published retrospective studies chronomodulated chemotherapy with oxaliplatin and FA/5-FU was used as neoadjuvant treatment for patients with unresectable colorectal liver metastases [25,26]. Therefore, combination regimens of irinotecan or oxaliplatin with FA/5-FU should be strongly considered as standard first-line chemotherapy for metastatic colorectal cancer [27,28].

Fig. 3



Quality of life assessed by the QLQ-C30 questionnaire. The quality of life was assessed after inclusion into the study and as often as possible during the course of treatment, using the EORTC-QLQ-C30 questionnaire, version 2. On this test, scores range from 0 to 100, divided according to points per item. Higher scores on global health status and physical functioning and lower scores on symptom scales and emotional functioning indicate a better quality of life.

At least for some patients with initially unresectable colorectal liver metastases it should be possible, through multidisciplinary efforts involving both surgeons and medical oncologists, to translate the antitumor activity of the new first-line regimens into long-term survival benefit.

In conclusion, the Saltz regimen given on an outpatient basis was safe and well tolerated in our study. Close monitoring of the patients and early aggressive treatment of side effects are essential, however, to prevent severe and potentially fatal gastrointestinal toxicity and thromboembolic events. As tumor control was achieved in about

75% and down-staging of metastatic disease was possible in some cases, combinations of CPT-11 and FA/5-FU should be further investigated in neoadjuvant protocols for initially unresectable liver metastases.

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