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Secondary treatment and predictive factors for second-line chemotherapy after first-line oxaliplatin-based therapy in metastatic colorectal cancer

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Abstract

Two consecutive studies have evaluated the efficacy of oxaliplatin combined with the Nordic bolus schedule of 5-fluorouracil and folinic acid as first-line treatment in metastatic non-resectable colorectal cancer. One hundred and twelve patients were followed after end of first-line treatment and any secondary therapy registered. Fifty-three patients (47%) did not receive second-line irinotecan-based chemotherapy. The main reason was too poor performance status (59%). These patients had a median survival of only 1.7 months after progression of first-line therapy. The best predictive factors at start of first-line chemotherapy for receiving later second-line chemotherapy were performance status and alkaline phosphatase level. Fifty-nine patients (53%) received irinotecan-based second-line therapy. Four (7%) patients had a partial response, and 28 (52%) had stable disease. Median progression-free survival after second-line chemotherapy was 4.1 months and median survival 9.5 months. Median survival after first-line chemotherapy and secondary liver surgery was 34 months and five-year disease-free survival 8%. Survival among patients receiving both first- and second-line chemotherapy was 20.8 months, but only 8.9 months in patients not receiving second-line irinotecan-based chemotherapy. Poor performance status or elevated alkaline phosphatase level at start of first-line chemotherapy predicts whether second-line chemotherapy will be given or not.

Systemic chemotherapy for metastatic colorectal cancer is often given as a combination of 5-fluorouracil (5FU) /folinic acid (FA) with irinotecan or oxaliplatin, and more recently also together with biological agents [1,2]. The optimal sequence of these chemotherapy agents is currently unclear. Despite the choice of initial therapy, exposure to each of these cytotoxic agents at some time over the course of a patient's disease has been associated with prolonged survival [3]. There is an ongoing discussion if combination chemotherapy always should be given as first-line therapy or if a sequential approach safely could be used [4]. Since there are no studies showing how to accurately predict which patients will fail to reach second-line treatment, current evidence supports the use of first-line combination chemotherapy. Second-line treatment options for these patients are evolving because of the expansion of treatment options available as first-line therapy. Some patients may have become eligible for surgical resection following effective first-line therapy, most receive second-line chemotherapy whereas some may not be able to tolerate or choose not to receive further chemotherapy.

In recent first-line chemotherapy studies in metastatic colorectal cancer, 30–40% of the patients are usually not treated with second-line chemotherapy [5]. As to our knowledge there are no studies describing the reasons for not giving second-line therapy or the survival of patients not fit for

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second-line therapy. There are also few studies on second-line irinotecan-based chemotherapy after progression on oxaliplatin-based chemotherapy [5]. In a randomised study, 62% of the patients who had received FOLFOX as first line therapy received protocol-based irinotecan chemotherapy together with infused 5FU (FOLFIRI) [6]. The effect was modest with a median progression-free survival of 2.5 months.

Shrinkage of tumours following chemotherapy may permit resection of some metastases initially considered unresectable. The definition of initial unresectability is the most critical aspect for interpreting results of secondary liver surgery. A recent consensus defined unresectability as: unresectable extrahepatic disease, more than 70% liver involvement, liver failure or being surgically unfit [7]. However, although there is clarity regarding absolute unresectability, there is variation among individual surgeons regarding borderline cases [8]. The possibility of secondary surgery after chemotherapy in initially unresectable metastatic hepatic disease was initially shown by Bismuth et al. [9]. It is still, however, uncertain if these patients will be moved prognostically from an expected very low 5-year survival rate to a 30% 5-year survival rate, or will recur after resection and have the same long-term prognosis as if they had not undergone resection.

We have in two consecutive studies given oxaliplatin together with 5FU/FA bolus (Nordic schedule) as first-line treatment to metastatic colorectal cancer patients [10,11]. The results showed the Nordic FLOX regimen to be highly active with a confirmed response rate of 46%, a median TTP of 7 months and a median survival of 16–18 months. The study population has been in follow-up after first-line treatment and any secondary therapy has been registered. This paper presents novel data concerning predictive factors at start of first-line chemotherapy for not receiving later second-line chemotherapy. It may therefore help clinicians in selecting patients that can safely be given sequential chemotherapy. It also presents novel data concerning the reasons for not giving any second-line chemotherapy and what survival these patients face. The effects of and survival after irinotecan-based second-line chemotherapy and secondary surgery are shown.

Patients and methods

Patients and treatment

All patients had prior histologically confirmed adenocarcinoma of colon or rectum, with non-resectable measurable metastatic disease. All patients had received the Nordic 5-FU/ FA bolus schedule combined with oxaliplatin (Nordic FLOX) as first-line treatment in two consecutive studies [10,11]. Fifteen patients (13%) initially judged unresectable were considered surgically resectable after chemotherapy and underwent secondary curative resections. The effect of secondary surgery on recurrence and survival was recorded. If a recurrence occurred, they were candidates for second-line chemotherapy. Registration of any second-line irinotecan-based therapy was done during follow-up after first-line treatment. All patients have been followed at least 5 years from start of first-line therapy. Fifty-nine patients were given second-line irinotecan based therapy. The regimens given were irinotecan combined with the Nordic 5FU/FA bolus schedule (FLIRI) (46%) [12,13], irinotecan monotherapy (27%), irinotecan with infused 5FU/leucovorin (FOLFIRI) (25%), and irinotecan with capecitabine (CAPIRI) (2%). Treatment was evaluated with CT scans every 8–9 weeks. The main reason for not giving second-line irinotecan-based therapy was reported. The study has been approved by the Ethical Committees in each country and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Study endpoints and statistical analyses

Response was calculated according to RECIST criteria [14]. The statistical analyses were performed with SPSS statistics package (v13.0, SPSS Inc. Chicago, USA). All statistical tests were two-tailed. The primary endpoint was receiving second-line irinotecan-based chemotherapy or not. As recommended by Harrel, the number of covariates was limited to 5–10% of the lowest group number [15]. Based on assessment of clinical importance [16], the following covariates were included in multiple logistic regression: poor performance status (WHO II), elevated white blood cell count ($\geq 10 \times 10^9$/l), elevated platelets count ($\geq 400 \times 10^9$/l), elevated alkaline phosphatase (≥ 300 U/l) and more than one organ lesion. Blood cell counts and serum biochemistry were measured within one week before start of first-line chemotherapy. For the end points progression free survival and survival, univariate analyses were performed using the Kaplan-Meier method.

Results

Patient characteristics

The demographic and baseline disease characteristics at start of first-line treatment are listed in Table I.

Table I. Patients' characteristics at start of first-line therapy.

Characteristics	No. of patients 112	%
Median age, Years (range)	60 (32–74)	
Gender		
Male	61	54
Female	51	46
WHO performance status		
0	54	48
I	43	38
II	15	14
Primary tumour site		
Colon	68	61
Rectum	43	39
Missing	1	
Prior adjuvant chemotherapy	16	14
Primary tumour resected	100	89
Organ involved		
Liver	87	78
Lung	35	31
Lymph node	31	28
Peritoneum	13	12
Other soft tissue	16	14
Bone	8	7
Other	13	10
Liver metastases only	31	28
No of organs involved		
1	42	38
2	43	38
≥3	27	24
Increased alkaline phosphatase (≥300 U/L)	64	58
Missing	2	
Increased platelets ($\geq 400 \times 10^9$/L)	34	30
Increased WBC count ($\geq 10 \times 10^9$/L)	35	31

Treatment or no second-line treatment

Fifty-three patients (47%) did not receive any second-line irinotecan based chemotherapy. The reasons were poor performance status (59%), declined further therapy (11%), toxicity during first-line therapy (9%), secondary surgery (7%), death (6%), second-line treatment with gemcitabine (4%) and radiotherapy (4%). Poor performance status and elevated alkaline phosphatase before start of first-line therapy were the best predictive factors for not receiving later second-line chemotherapy. The results of the multivariate analysis on later second-line chemotherapy are shown in Table II.

Overall, 59 patients (53%) received irinotecan-based second-line therapy. Median time from progression on first-line therapy to start of second-line therapy was 36 days (range 1–549 days). Among the eleven patients who had progressive disease as best response on first-line therapy, only two patients (18%) received second-line therapy. Eight patients with recurrence after secondary surgery were considered for second-line irinotecan-based chemotherapy, one declined but the rest were in good performance status and received therapy. Reasons to stop second-line chemotherapy were progression (73%), toxicity (14%), prolonged stabilisation (3%), secondary radical stereotactic irradiation (3%), patient refusal (3%), death (2%) and radiation therapy (2%). Among the eight patients where treatment had to be stopped due to toxicity, three received FOLFIRI (20% of the FOLFIRI treated), one CAPIRI (all treated), one FLIRI (4% of the FLIRI treated) and three irinotecan monotherapy (19% of monotherapy treated).

Table II. Results from multiple logistic regression analyses assessing influence of baseline characteristics at start of first-line therapy on risk for not receiving second-line therapy.

	OR[a]	p
WHO performance status II vs. 0–I	7.5	*0.01*
Alkaline phosphatase >300 U/l vs. ≤300 U/l	2.5	*0.05*
White blood cell count $>10 \times 10^9$/l vs. $\leq 10 \times 10^9$/l	1.1	*0.83*
Platelets $>400 \times 10^9$/l vs. $\leq 400 \times 10^9$/l	1.0	*0.96*
2 or more organs involved vs. one organ	1.1	*0.77*

[a]Odds ratio. Serum alkaline phosphatase measured by IFCC (International Federation of Clinical Chemistry) method, normal range 90–285 U/l.

Survival of non-second-line treated patients

The median survival in 50 patients progressing after first-line chemotherapy and not receiving second-line irinotecan-based chemotherapy was 2.4 months (95% CI 1.3–3.5 months). In the subgroup who did not receive second-line irinotecan-based chemotherapy because of poor performance status median survival was 1.7 months (95% CI 1.0–2.4 months). Fifty-eight percent of these patients were dead within 2 months, 74% within 3 months, and 84% within 4 months. Six patients who themselves decided not to have second-line irinotecan therapy had a median survival of 7.4 months after progression on first-line therapy. Three patients with secondary surgery were alive at 5 years without progression/recurrence of disease. Median survival from start of first-line therapy among all patients not receiving irinotecan-based second-line chemotherapy was 8.9 months.

Response and survival of irinotecan-treated patients

Fifty-four patients receiving irinotecan based second-line therapy were evaluable for response; five patients stopped treatment before the first evaluation due to toxicity. Four patients had a partial

response (7%), 28 had stable disease (52%) and 22 progressive disease (41%). The percentage of PR/SD in patients receiving FLIRI was 60% (PR 2/13), FOLFIRI 47% (PR 1/4), CAPIRI (all) (PR 0/1) and monotherapy 69% (PR 1/10). Both patients who had progressive disease as best response on first-line therapy achieved stable disease on second-line therapy. Four of the patients stopping treatment early due to toxicity reported no progression date, but only a late date of death. These patients were judged not evaluable with regard to progression-free survival. Fifty-five patients were evaluable with regard to progression-free survival. Median progression-free survival (PFS) after start of second-line therapy was 4.1 months (95% CI 2.7–5.6 months). Median PFS of patients with a SD was 6.5 months (range 2.4–26.3 months). Median survival in all patients (n = 59) after start of second-line irinotecan therapy was 9.5 months (95% CI 6.5–12.4 months). One year after start of second-line therapy, 14 (24%) of the 59 patients were alive. Among the seven patients with recurrence after secondary surgery, median PFS was 8.2 months and median survival 24.5 months after start of irinotecan-based second-line therapy. Median survival from start of first-line therapy among the patients receiving both first- and second-line chemotherapy was 20.8 months.

Outcome after secondary surgery

Median survival of the 15 patients undergoing secondary curative surgery from start of first-line therapy was 41 months. One patient was reconsidered to be resectable initially, and had liver resection after three courses of chemotherapy and is alive without disease 5 years after surgery. One patient who had a locally inoperable advanced colon cancer with peritoneal carcinomatosis, obtained a partial response after eight courses and was subject to radical second look operation, and is alive without disease 6 years after surgery. One patient had lung resection after response to chemotherapy, and is alive at 5 years with recurrence. Twelve patients with initially non-resectable liver disease had liver resection after response to chemotherapy. Median survival after start of first-line chemotherapy of these patients is 34 months. One patient is alive after 5 years after surgery without recurrence (5 years disease-free survival 8%). Nine of the liver-resected patients died from recurrence of disease, two died from postoperative complications.

Discussion

As we have been unable to accurately predict which patients will fail to reach second-line treatment, current evidence has supported the use of combination chemotherapy in first-line treatment [4]. Patients with cancer-induced poor performance status is a group in whom it may be more crucial to use first-line combination chemotherapy, as they, without rapid tumor response, are at high risk of being unable to proceed with a potentially active second-line option. Poor performance status and elevated alkaline phosphatase are among the factors indicating a worse prognosis in metastatic colorectal cancer patients treated with 5-FU, oxaliplatin or irinotecan [16–18]. We have previously shown that patients with normal alkaline phosphatase and platelet levels at baseline had a median survival of 23 months after first-line chemotherapy, whereas it was 10 months if both levels were elevated [10]. In the present study the best predictive factors to whether a patient would not receive any second-line chemotherapy was poor performance status and elevated alkaline phosphatase level at start of first-line therapy. In such patients a sequential approach may not be advisable. These patients should thus be considered for combination therapy as first-line chemotherapy, or possibly an experimental fast sequential approach including all available drugs.

There are almost no studies showing the reasons for not giving second-line chemotherapy in metastatic colorectal cancer and the fate of the patients not fit for further chemotherapy. In the Tournigand study patients did not receive second-line therapy as a consequence of death, poor performance status or refusal, but no further data were given [6]. In our follow-up, 53 patients (47%) did not receive any second-line irinotecan based chemotherapy, and the main reason for this was poor performance status. The median survival after progression on first-line therapy among these patients with such a poor performance status was 1.7 months. The decision not to give second-line chemotherapy in these patients therefore seems reasonable, as one would not expect much effect of chemotherapy on survival. The results illustrate that the clinician's judgement of the performance status is quite good for selecting patients not to receive second-line chemotherapy.

Second-line chemotherapy in metastatic colorectal cancer has an impact on survival. In the two second-line studies using irinotecan as single agent after 5FU failure, survival benefit ranged between 2 to 3 months [19,20]. A similar benefit was found when oxaliplatin and fluorouracil-leucovorin was given as second-line therapy after irinotecan and 5-fluorouracil-leucovorin [21]. There have been published six previous studies on second-line irinotecan-based chemotherapy after progression on oxaliplatin-based chemotherapy (Table III). Most studies have found disease stabilisation in 60–70% of the patients, a

Table III. Results from studies on effect of irinotecan-based second-line chemotherapy in metastatic colorectal cancer patients previously treated with oxaliplatin.

	Patient accrual	Line of treatment	n	% PR	% PR/SD	Median PFS (months)	Median Survival (months)
Tournigand et al. [6]	From 1-line study	2nd	69	4	55	2.5	
Ulrich-Pur et al. [22]	Phase II	2nd	38	21	71	4.8	>9.5
Stickel et al. [23]	Retrospective	2nd+3rd	26	27	62	5.8	10
Recchia et al. [24]	Phase II	2nd+3rd	35	20	69	7.1	14
Mabro et al. [25]	Phase-II	2nd+3rd	29	17	69	4.1	9.7
Mabro et al. [26]	Phase II	2nd+3rd	65	23	60	4.7	10.5
Sørbye et al.	From 1-line study	2nd	59	7	59	4.1	9.5

PFS of 4–6 months and a median survival of about 10 months. Our study has a design best comparable to the Tournigand study as it registered second-line chemotherapy in an ongoing first-line study, and there is no mixture of second- and third-line treatment. The selection bias should be less in our and the Tournigand study than in the phase II studies, and might better reflect the population where second-line therapy is to be used. The results from our study reveal, as the Tournigand study, a low response rate, but a stabilisation/regression after progression in 59% of the patients. Our study showed a median progression-free survival after start of second-line therapy of 4.1 months and a median survival of 9.5 months. Irinotecan-based second-line chemotherapy after oxaliplatin resistance therefore seems effective and at least of some benefit to more than half of the patients.

In a combined analysis of seven recent randomised phase III trials, median overall survival was correlated to the proportion of patients having received all three drugs (FU/FA, irinotecan, and oxaliplatin [3]. There are studies where 80% of the patients were able to receive second-line chemotherapy [3]. Criticism has been raised towards studies where second-line chemotherapy is "only" given to 60% of the patients [27]. Median survival among the patients in our study receiving both first- and second-line chemotherapy was 20.8 months, but only 8.9 months in patients not receiving second-line irinotecan-based chemotherapy. This difference in survival is not only due to lack of second-line chemotherapy. It rather indicates that patients receiving second-line chemotherapy had a better prognosis initially than patients not receiving such therapy.

Systemic chemotherapy can downsize a proportion of initially unresectable liver metastases to the point of resectability. It is recognised that the criteria for resectability of liver metastases vary, in part reflecting the experience of the surgeon. Secondary surgery after preoperative chemotherapy for non-resectable colorectal liver metastases has shown a 5-year survival for this down-sized group of 40%, with the survival curve almost replicating that of patients who had initially resectable disease and underwent immediate surgery (9). These data have recently been updated after a mean follow-up of 49 months, with 111 patients (80%) developing tumor recurrence [28]. Survival was 33% at 5 years with a disease-free survival of 22% (at 10 years 17%). Recently a prospective, multicentre study where oxaliplatin, 5 FU and leucovorin were given to patients with unresectable liver-only metastasis from colorectal cancer was published [28]. The recurrence rate for the 14 patients who underwent complete resection was 71% and at a median follow-up of 36 months, 67% were alive. In a retrospective analysis of the multicentre N9741 study, 24 patients with initially unresectable metastatic colorectal cancer had undergone secondary curative metastatic resection [29]. With a median follow-up of 34 months, 14 patients are alive (58%) and seven patients (29%) remain disease-free. Median survival in resected patients was 42 months. Interestingly, 42 patients achieving complete response with chemotherapy and who did not undergo resection had a median time of survival of 39 months. Seven patients in our study with recurrence after secondary surgery could all start second-line chemotherapy, and they had a much better progression free survival (median 8.2 vs. 4.1 months) and survival (median 24.5 vs. 9.5 months) after second-line chemotherapy than the other patients. Patients able to have secondary surgery after a good response to chemotherapy may represent a better prognostic group. In our study only one of 12 patients with a secondary liver surgery was alive without disease after five years (8%). It seems that an aggressive surgical approach to the treatment of patients with initially unresectable liver metastasis who become resectable after chemotherapy is reasonable. There is still, however, uncertainty of how much secondary surgery

contributes to survival and long-term disease-free survival.

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