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ORIGINAL ARTICLE

Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a phase II study in colorectal cancer patients with non-resectable liver metastases

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Abstract
Purpose To assess the rate of R_0 resection of liver metastases achieved after chemotherapy with FOLFIRINOX.
Patients and methods Patients with histologically proven primary colorectal cancer and bidimensionally measurable liver metastasis, not fully resectable based on technical inability to achieve R_0 resection, but potentially resectable after tumor reduction, were given FOLFIRINOX: oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², bolus fluorouracil 400 mg/m² and fluorouracil 46-h continuous IV infusion 2,400 mg/m², every 2 weeks for a maximum of 12 cycles.
Results Thirty-four patients were enrolled. Response rate before surgery was 70.6% (95%CI: 52.5–84.9). Twenty-eight patients (82.4%) underwent hepatic resection and nine achieved R_0 resection [26.5% (95% CI: 12.9–44.4%)]. The rate of clinical complete remission after surgery was 79.4%. Two-year overall survival was 83%.
The most frequent grade 3 or 4 toxicities were neutropenia (64.8%), diarrhea (29.4%), fatigue (23.5%), abdominal cramps (14.7%), neuropathy and nausea (11.8% each), and AST/ALT elevation (14.7/11.8%). Only one patient experienced febrile neutropenia, four patients withdrew due to toxicity and no toxic death was observed.
Conclusion FOLFIRINOX, with an acceptable toxicity profile, shows a high response rate in liver metastases from colorectal cancer. The rate of hepatic resection in patients initially not resectable, is attractive and warrants further assessment of this regimen in randomized studies compared to standard regimens.

Keywords Colorectal cancer · Liver metastases · Hepatic resection · Irinotecan · Fluorouracil · Oxaliplatin · Tritherapy

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Introduction

About 25% of patients with colorectal cancer have synchronous liver metastases [1] and an additional 30–40% will develop metachronous metastases [2]. The liver is a unique metastatic site in 30–60% of patients with metastases [3, 4]. The only curative attempt for patients with metastatic disease confined to the liver is hepatic resection, which achieves a 20–45% 5-year survival [5–8] that appears to further plateau off, whereas virtually all patients without resection will eventually die due to tumor progression

within 5 years [9, 10]. However, about only one-fourth to one-third of patients with isolated liver metastases can benefit of liver resection with a curative intent (R_0 resection) [4, 11]. In patients with unresectable liver metastases, systemic chemotherapy is the standard treatment option. It has been shown to permit potentially curative resection following tumor shrinkage in a percentage of patients varying from 3.3 to 40.9% across published series [11]. Standard doublet regimens consisting of fluorouracil plus either irinotecan or oxaliplatin have dramatically increased the response rate achieved with fluorouracil/leucovorin (5-FU/LV) alone from 22 to 35–54% in metastatic colorectal cancer [12–14]. Subsequently, more patients can now benefit of hepatic resection after chemotherapy-induced downstaging. Moreover, it has been suggested that resection rate is correlated to objective response rate to chemotherapy [15]. It was therefore appealing to assess a tritherapy regimen with fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) in selected patients in order to further increase response rate and/or the magnitude of tumor reduction and ultimately the rate of patients with R_0 hepatic resection. We first tested the feasibility and recommended dose of FOLFIRINOX in a phase I study [16]. The recommended dose of irinotecan and oxaliplatin in combination with full dose 5-FU/LV was 180 and 85 mg/m², respectively. The antitumor activity was high in gastrointestinal malignancies with an acceptable safety profile. Thus, we performed the present phase II study.

Patients and methods

Study objectives

The primary objective was the rate of R_0 resection of liver metastases achieved after FOLFIRINOX chemotherapy. Secondary objectives were overall response rate, radiological complete response rate after surgery, overall survival (OS) and safety.

Patient selection

Patients had to fulfill all the following eligibility criteria: histologically proven and fully resected primary colorectal cancer; at least one bidimensionally measurable liver metastasis ≥20 mm on CT-scan; exclusive liver metastases or associated with one resectable lung metastasis; non fully resectable metastases based on technical inability to achieve R_0 resection (i.e. those involving right or left hepatic pedicle and coming into contact with contra lateral pedicle, or involving or coming into contact with vena cava, or involving two hepatic veins and coming into contact with the third one, or those that would leave <25% of functional liver after resection); only one previous chemotherapy regimen (without irinotecan or oxaliplatin) given in the adjuvant or metastatic setting; age 18–70 years; World Health Organization (WHO) performance status (PS) < 2; neutrophils count $\geq 1.5 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; serum bilirubin <1.5 × upper normal limit (UNL); AST, ALT and alkaline phosphatase ≤3 × UNL; serum creatinine ≤120 μmol/l or creatinine clearance ≥60 ml/min; previous surgery, radiation therapy or chemotherapy completed at least 4 weeks (8 weeks for extensive pelvic radiation) prior to study treatment initiation; written informed consent.

Non-eligibility criteria were: Patients not candidates for hepatic resection even after major tumor shrinkage; history of another cancer (except curatively resected non-melanoma skin cancer or in situ cervical carcinoma); National Cancer Institute of Canada-Common Toxicity Criteria (NCIC-CTC) grade >1 peripheral neuropathy; intestinal obstruction or sub-obstruction; history of inflammatory bowel disease or extensive intestinal resection; severe concomitant medical condition that could hamper patient's compliance; administration of another investigational therapy within 4 weeks prior to study treatment initiation; concomitant anticancer therapy; pregnant or breast-feeding women; patients of both genders with reproductive potential not using adequate contraception.

Study treatment

Oxaliplatin (Eloxatin™, Sanofi-Aventis, Paris, France) at 85 mg/m² was delivered as a 2-h IV infusion immediately followed by irinotecan (Campto™, Pfizer, Paris, France) at 180 mg/m² over a 30–90 min IV infusion. Leucovorin at 400 mg/m² over a 2-h IV infusion could start during or after irinotecan infusion and was followed by bolus fluorouracil at 400 mg/m² and fluorouracil at 2,400 mg/m² over a 46-h continuous IV infusion. Cycles were repeated every 2 weeks for a maximum of 12 cycles, or until disease progression, intolerable toxicity or patient's refusal. Prophylactic G-CSF support was permitted from the first cycle. Cycles could be delayed as long as neutrophils were $<1.5 \times 10^9$/l or platelets $<80 \times 10^9$/l. If these values were not recovered at day 28, the patient had to go off study. In case of febrile neutropenia or grade 4 neutropenia lasting >7 days, G-CSF was given at further cycles if not already given. If these events occurred on G-CSF, or in case of grade 3–4 diarrhea, irinotecan dose was reduced to 150 mg/m². If the events recurred, oxaliplatin dose was reduced to 60 mg/m². In case of grade 3–4 thrombocytopenia or grade 2 neuropathy, only the oxaliplatin dose was reduced and in case of grade 3–4 mucositis, hand-foot syndrome or conjunctivitis, only the 5-FU dose was reduced by 25%.

In case of hepatic resection, study treatment was to be interrupted for 3–8 weeks before and 3–6 weeks after surgery.

Assessment

Physical examination/biological workup and tumor assessment by spiral abdominopelvic and thoracic CT-scan were to be performed within 8 and 14 days, respectively, prior to study treatment initiation. Non-resectability of liver metastases at baseline was determined by an independent expert panel including two liver surgeons and two radiologists. This committee was set up during study and retrospectively determined resectability. Tumor measurements according to WHO criteria were to be repeated every 8 weeks and reviewed by the multidisciplinary committee in each center. In case of hepatic resection, an additional tumor assessment was to be performed within 4 weeks after surgery. In case of quick tumor regression on chemotherapy, it was advised to perform resection before complete radiological response. If some lesions could not be fully resected, radiofrequency or cryo-ablation could be performed at the surgeon's discretion. Such patients might be accounted as radiological complete response, but categorized as R_x resection. R_0 resection was defined as free margin $\geq$2mm. After study treatment discontinuation, patients were to be followed up every 3 months until death.

Statistical considerations

Using Simon's minimax design with a 5% α risk and 85% power, 36 patients were necessary to allow a conclusion of insufficient activity in terms of R_0 resection ($p0 < 20\%$). Survival rates were estimated according to Kaplan–Meier method.

The analysis was performed on the intent-to-treat population. Adverse events were graded according to NCIC-CTC version 2.

Results

Patients

Thirty-four patients were enrolled in five centers from November 11, 2000 to May 21, 2003. All were treated and evaluable for efficacy and safety. Eleven patients had minor protocol violations, but were included in the analysis: one had liver function tests outside accepted values, one had peritoneal metastases, and one had received prior irinotecan-based chemotherapy. Only one patient was considered to have initially resectable lesions according to the independent expert panel. Baseline characteristics of the 34 enrolled patients are summarized in Table 1. The median age was 58 years (range: 39–69), 65% of patients were male and 56% had PS 0. Twenty-one patients (62%) were metastatic at diagnosis. Five patients had one potentially concomitant resectable lung metastasis at baseline. Thirteen patients (38%) had received prior chemotherapy, 11 of them as adjuvant therapy. Five patients had undergone prior hepatic resection, including two after reductive chemotherapy. Grade 1 or 2 abnormal biological values were: anemia in 35% of patients, elevated lactate dehydrogenase in 41%, hyperleukocytosis in 5.9% and elevated liver function tests including alkaline phosphatase in 47%.

Table 1 Baseline patient characteristics ($N = 34$)

Median age (range)	58 years	(39–69)
Gender		
Male	22	(64.7%)
Female	12	(35.3%)
WHO performance status		
0	19	(55.9%)
1	12	(35.3%)
Unknown	3	(8.8%)
Primary tumor		
Colon	28	(82.4%)
Rectum	6	(17.6%)
Liver metastases		
Synchronous	21	(61.8%)
Diagnosed ≤6 months after primary tumor	1	(2.9%)
Diagnosed >6 months after primary tumor	12	(35.3%)
Organs involved		
Liver	34	(100.0%)
Lung	5	(14.7%)
Peritoneum	1	(2.9%)
Previous surgery		
Primary tumor	34	(100.0%)
Hepatic resection	5	(14.7%)
Colostomy	8	(23.5%)
Radiation therapy	4	(11.8%)
Chemotherapy		
Adjuvant	11	(32.4%)
For metastatic disease	2	(5.9%)
Resectability (as per independent multidisciplinary committee)		
Initially resectable	1	(2.9%)
Non resectable, even after downstaging	7	(20.6%)
Non initially resectable, but potentially resectable after downstaging	26	(76.5%)

Exposure to study treatment

Three hundred and eleven cycles of chemotherapy were delivered with a median of 9.5 cycles per patient (range: 4–12). The median number of cycles given before surgery was 6.5 (range: 4–12). Twenty-one patients (75% of operated patients) continued to receive study treatment after surgery with a median of four cycles per patient (range: 1–8). Seventeen patients (50%) did not receive tritherapy over 61 cycles: 16 patients stopped oxaliplatin after 1–10 cycles and five irinotecan after 6–9 cycles. The vast majority of cycles with drugs omitted were given after surgery. Before surgery, the median relative dose intensity (RDI) of irinotecan, oxaliplatin and fluorouracil were 0.87 (0.65–1.01), 0.88 (0.44–1.01) and 0.91 (0.70–1.08), respectively. Thirty patients (88.2%) had at least one cycle delayed and 27 (79.4%) had at least one dose reduction. Irinotecan dose was reduced in 14 patients and oxaliplatin in 13. The main reasons for dose reduction were diarrhea and neuropathy, while the main reason for dose delay was neutropenia. Twenty-four patients (70.6%) were given G-CSF, including six (17.6%) as primary prophylaxis. Reasons for study treatment discontinuation before 12 cycles were: decision to stop chemotherapy after surgery in 13 patients (38.2%), progressive disease in 3 and toxicity in 3. One additional patient withdrew for toxicity at the 12th cycle.

Efficacy

The overall response rate before surgery, as determined by the independent committee, was 70.6% (95% CI: 52.5–84.9) in the treated population, including one non-confirmed complete response (CR), 18 partial responses (PR) and 5 non-confirmed PR (Table 2). In addition, six patients (17.7%) had minor responses (mR), including two patients with tumor shrinkage of 48–49%. Of note, only three patients (8.8%) had progressive disease as best response. Twenty-eight patients (82.4%) underwent hepatic resection. The reasons for non-resection were progressive disease for three patients and insufficient downstaging despite PR or mR for the other three. Three patients underwent two successive resections. Resected patients consisted of 22/24 responding patients plus five minor responses and one SD. The latter patient was deemed initially resectable. The median time between treatment initiation and surgery was 4 months (range: 2–7). Fifteen patients (53.6%) underwent conventional resection only, eight (28.6%) surgery + radiofrequency, two surgery + cryo-ablation and three (10.7%) cryo-ablation only. Nine patients achieved R_0 resection corresponding to 26.5% (95%CI: 12.9–44.4%) of the whole population. Among R_0 patients, 4 had margins > 1 cm. Thirteen patients (38.2%) were Rx, due to radiofrequency or cryo-ablation. The rate of radiological complete remission after surgery was 79.4% of the treated population. With a median follow-up of 31 months, eight of the nine patients with R_0 resection relapsed (seven in the liver, one in the lung) with a median RFS of 13.9 months (range: 10.6–25.6). Only 11 patients died and the 2-year overall survival estimate was 83% (95% CI: 63–93%). Median survival is estimated at 36 months (95% CI: 27-not reached) (Fig. 1)

Table 2 Response rate to FOLFIRINOX (WHO criteria)

	ITT population ($N = 34$)	
Non-confirmed CR	1	(2.9%)
PR	18	(52.9%)
Non-confirmed PR	5	(14.7%)
Minor responses	6	(17.7%)
Stable disease	1	(2.9%)
Progressive disease	3	(8.8%)
Overall response rate	70.6% (95% CI: 52.5–84.9)	

CR complete response, *PR* partial response

Safety

All 34 treated patients experienced at least one treatment-related adverse event (AE) and 26 (76.5%) at least one grade 3 or 4 related AE. Main toxic events are summarized in Table 3. Neutropenia, diarrhea, nausea, peripheral neuropathy, fatigue, vomiting, cholinergic syndrome, mucositis, alopecia and transient elevation of AST/ALT were the most frequent AEs, occurring in ≥50% of patients. The most frequent grade 3 or 4 toxicities were neutropenia (64.8%), diarrhea (29.4%), fatigue (23.5%), abdominal cramps (14.7%), neuropathy and nausea (11.8% each), and

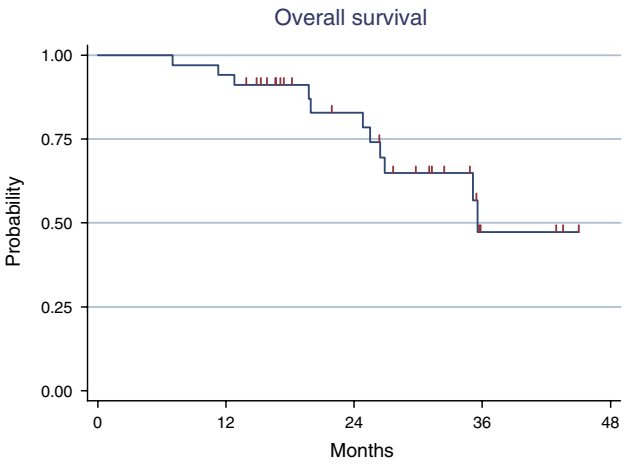

Fig. 1 Overall survival ($N = 34$). Events: 11, censored: 23, 2-year probability: 83% (95% CI: 63–93%), median: 35.5 (95% CI: 26.9-not reached)

Table 3 Treatment-related adverse events and biological toxicities by patients ($N = 34$)

	All grades		Grade 3		Grade 4	
Diarrhea	31	(91.2%)	10	(29.4%)	0	–
Nausea	31	(91.2%)	4	(11.8%)	0	–
Neuropathy	29	(85.3%)	4	(11.8%)	0	–
Fatigue	28	(82.4%)	8	(23.5%)	0	–
Vomiting	27	(79.4%)	1	(2.9%)	1	(2.9%)
Cholinergic syndrome	22	(64.7%)	0	–	0	–
Mucositis	17	(50.0%)	0	–	0	–
Alopecia	16	(47.1%)	NA	–	0	–
Anorexia	11	(32.4%)	2	(5.9%)	0	–
Epistaxis	9	(26.5%)	0	–	0	–
Rhinitis	7	(20.6%)	0	–	0	–
Abdominal pain	3	(8.8%)	0	–	0	–
Abdominal cramp	14	(41.2%)	5	(14.7%)	0	–
Neutropenia	33	(97.1%)	11	(32.7%)	11	(32.3%)
Febrile neutropenia	1	(2.9%)	0	–	1	(2.9%)
Thrombocytopenia	15	(44.1%)	1	(2.9%)	0	–
Anemia	29	(85.3%)	1	(2.9%)	0	–
AST elevated	22	(64.7%)	5	(14.7%)	0	–
ALT elevated	20	(58.8%)	4	(11.8%)	0	–
Bilirubin elevated	6	(17.6%)	2	(5.9%)	0	–

NA not applicable, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

AST/ALT elevation (14.7/11.8%). One half of patients had to discontinue at least one drug before study end. Ninety-four percent of them discontinued oxaliplatin due to cumulative neuropathy. Grade 4 events were observed only for neutropenia (32.4%) and vomiting (2.9%), but only one episode of febrile neutropenia occurred at cycle 1. Four patients discontinued therapy due to toxic events: one grade 3 neutropenia with grade 2 diarrhea, two grade 2 neuropathy, (one combined with grade 2 asthenia) and one sub-obstructive syndrome with abdominal cramps and esophagitis.

Discussion

This is the first phase II study exploring this schedule of tritherapy in CCRM. The aim of our trial was to assess the clinical activity of the FOLFIRINOX regimen, combining all three active cytotoxic agents in patients with unresectable liver metastases from colorectal cancer in terms of resectability with curative intent. This study enrolled selected patients with isolated or prevalent liver metastases and stringent criteria for non-resectability, but amenable to secondary resection in case of sufficient tumor downstaging. In this multicenter study, non-resectability criteria were to be retrospectively validated by an independent committee. The response rate achieved by FOLFIRINOX was 70.6% (95% CI: 52.5–84.9) in the overall population. This high response rate compares favorably with response rates achieved with conventional doublet regimens in patients with either non-selected metastatic disease (from 35 to 54%) [12–14], or isolated liver metastases and similar non-resectability criteria (from 48 to 59%) [15]. It is worth noting that, in our study, one CR and 5 PR were not confirmed at least 4 weeks apart, as requested by WHO criteria because timing of hepatic resection did not justify waiting for radiological confirmation. Moreover, the protocol recommended performing resection before achieving complete response in order to facilitate surgical location of metastases for adequate resection. Furthermore, it is unlikely that a significantly lower response rate would have been observed if all major responses had been confirmed [18].

Five other studies have already tested 3-drug regimens with various schedules and doses in metastatic colorectal cancer (Table 4). Three studies combined the three drugs together every 2 weeks [19, 20, 23], while two used weekly 5-FU with alternated irinotecan and oxaliplatin every other week [21, 22]. The planned dose intensity of irinotecan and oxaliplatin was lower with alternating schedules. The observed response rates varied from 45 to 78%, probably due to various patients' selection criteria, including pretreatment status and metastatic location. Table 4 also suggests there could be a trend for higher response rate with regimens delivering the highest dose intensity. Not only objective responders could benefit of liver resection but also some patients with mR. In bulky tumor indeed, mR may correspond to significant tumor shrinkage and allow resection. Thus, as many as 82.4% of patients were resected and 79.4% achieved a postoperative radiological CR. This rate of secondary resection compares favorably with that observed (33–36%) after conventional 2-drug regimens [17, 24] and is also higher than that reported (50%) in 22 comparable patients with isolated, unresectable liver metastases treated with tritherapy [19]. In turn, the rate of R_0 resection achieved in our study (26.5% in the treated population and 34.6% in the target population) is similar to that reported (33–41%) with 2- or 3-drug regimens [17, 19, 24]. These results are in line with the finding that overall resection rate, but not R_0 rate, is correlated with objective response rate to chemotherapy [15]. Thus, the criterion of "non-resectability even after downstaging" is subjective, especially when a new regimen is tested. We advise that such a criterion be withdrawn in comparative phase III trials focused on resectability rate in unresectable patients.

The safety profile of our triplet regimen was acceptable in this selected population and appears to merely consist of the addition of drug-specific toxicities. No unexpected toxicity occurred. Although primary prophylaxis with G-CSF was permitted by protocol, few investigators used

Table 4 Three-drug regimens in metastatic colorectal cancer

Author (reference)	Study phase Planned dose intensity (mg/m² per week)	Patient selection	*N* patients	Response rate (%)	Overall resection rate (%)	R_0 resection (%)
Ychou (present study)	Phase II Iri: 90 Oxa: 42.5 5-FU bolus: 200 5-FU CIVI: 1,200	Isolated, or prevalent unresectable liver mts, but potentially resectable after downstaging	34	70.6	82.4	26.5
De la Camara [19]	Phase II Iri: 75 Oxa:30 5-FU CIVI: 1,300	Isolated, unresectable liver mts or poor prognostic factor after surgery	39 (22 unresectable)	64 NA	59.0 50.0	48.7 40.9
Falcone [20]	Phase I Iri: 62.5–87.5 Oxa: 50 5-FU CIVI: 1,900 Phase II Iri: 82.5 Oxa: 42.5 5-FU CIVI: 1,600	Unselected, unresectable mts (not only liver)	42 32	71 72	40.5[a]	25.7[a]
Seium [21]	Phase I–II Iri: 32–56 Oxa: 28–34 5-FU CIVI: 1,840	Unselected metastatic disease (not only liver)	30	78	23.3	NA
Cals [22]	Phase I Iri: 24–40 Oxa: 16–32 5-FU CIVI: 2.080–2,400	Unselected metastatic disease (not only liver)	34	50%	14.7%	NA
Souglakos [23]	Phase III Iri: 75 Oxa: 32.5 5-FU bolus: 400 5-FU CIVI: 600	Unselected metastatic disease (not only liver)	101	45	NA	NA

Iri irinotecan, *Oxa* oxaliplatin, *5-FU* 5-fluorouracil, *CIVI* continuous IV infusion, *mts* metastases, *NA* not applicable/not available

[a] For both phase I and II parts

it. Yet febrile neutropenia seldom occurred in only one patient. Of note, most drug omissions were done after surgery, in addition to 25% of operated patients who did not receive chemotherapy anymore, when the theoretical benefit of tritherapy (supposed to increase resection rate) was lost.

In conclusion, FOLFIRINOX appears to be a safe and very effective regimen in selected patients with isolated or prevalent unresectable liver metastases, but who are treated with a curative intent. This regimen deserves to be assessed in randomized trials versus standard doublet regimens.

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References

1. Bengmark S, Hafstrom L (1969) The natural history of primary and secondary malignant tumors of the liver. I. The prognosis for patients with hepatic metastases from colonic and rectal carcinoma by laparotomy. Cancer 23:198–202
2. Welch JP, Donaldson GA (1979) The clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg 189:496–500
3. Weiss L, Grundmann E, Torhorst J et al (1986) Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1,541 necropsies. J Pathol 150:195–203
4. Zadavski KE, Lee YTM (1994) Liver metastases from colorectal carcinoma: incidence, resectability and survival results. Ann Surg 60:929–932
5. Hughes KS, Simon R, Songhorabodi S et al (1986) Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. Surgery 100:278–284
6. Nordlinger B, Jaeck D, Guiguet M et al (1992) Surgical resection of hepatic metastases. Multicentric retrospective study by the French association of surgery. In: Nordlinger B, Jaeck D (eds) Treatment of hepatic metastases of colorectal cancer. Springer, Berlin, pp 129–146
7. Lorenz M, Muller HH, Schramm H et al (1998) Randomized trial of surgery versus surgery followed by adjuvant hepatic arterial

infusion with 5-fluorouracil and folinic acid for liver metastases of colorectal cancer. German cooperative group on liver metastases (Arbeitsgruppe Lebermetastasen). Ann Surg 228:756–762
8. Schelle J, Stangl R, Altendorf-Hofman A et al (1995) Resection of colorectal liver metastases. World J Surg 19:59–71
9. Bengtsson G, Carlsson G, Hafström Larsolof L et al (1981) Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg 141:586–589
10. Wagner JS, Adson MA, Van Heerden JA et al (1984) The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment. Ann Surg 199:502–508
11. Leonard GD, Brenner B, Kemeny NE (2005) Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. J Clin Oncol 23:2038–2048
12. Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone: a multicentre randomised trial. Lancet 355:1041–1047
13. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
14. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
15. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH (2005) Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. Ann Oncol 16:1311–1319
16. Ychou M, Conroy T, Seitz JF et al (2003) An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. Ann Oncol 14:481–489
17. Pozzo C, Basso M, Cassano A et al (2004) Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. Ann Oncol 15:933–939
18. Perez-Gracia JL, Munoz M, Williams G et al (2005) Assessment of the value of confirming responses in clinical trials in oncology. Eur J Cancer 41:1528–1532
19. de la Camara J, Rodriguez J, Rotellar F, et al (2004) Triplet therapy with oxaliplatin, irinotecan, 5-fluorouracil and folinic acid within a combined modality approach in patients with liver metastases from colorectal cancer. Proc Am Soc Clin Oncol 23:268, 3593A
20. Masi G, Cupini S, Marcucci L et al (2006) Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. Ann Surg Oncol 13:58–65
21. Seium Y, Stupp R, Ruhstaller T et al (2005) Oxaliplatin combined with irinotecan and 5-fluorouracil/leucovorin (OCFL) in metastatic colorectal cancer: a phase I–II study. Ann Oncol 16:762–766
22. Cals L, Rixe O, Francois E et al (2004) Dose-finding study of weekly 24-h continuous infusion of 5-fluorouracil associated with alternating oxaliplatin or irinotecan in advanced colorectal cancer patients. Ann Oncol 15:1018–1024
23. Souglakos J, Androulakis N, Syrigos K et al (2006) FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomized phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer 94(6):798–805
24. Alberts SR, Horvath WL, Sternfeld WC et al (2005) Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. J Clin Oncol 23:9243–9249