Abstract. Background: To evaluate a strategy combining high-dose 5FU-irinotecan-leucovorin (HD-FOLFIRI) chemotherapy, radiofrequency ablation and surgery in patients with unresectable liver metastases from colorectal cancer. Patients and Methods: Patients, all presenting UDP glucuronosyl transferase-1A1 (UGT1A1) 6/6 or 6/7 genotype, received HD-FOLFIRI (with high-dose irinotecan: 260 mg/m²), one cycle every two weeks. The feasibility of local therapy (surgery and/or radiofrequency) was assessed every four cycles. The objective of therapy was the complete clearance rate of metastases. Results: The trial was terminated after inclusion of 18 out of the 40 planned patients due to insufficient recruitment. The median number of metastases was seven (range=2-30). On intention-to-treat analysis, six patients (33.3%) received local treatment of metastases with complete clearance of metastases in each case. Median progression-free and overall survivals were 15.3 months and 33.7 months, respectively. Conclusion: The assessed strategy is feasible and allows for a complete clearance of metastases in one third of patients, with prolonged survival.

The 5-year mortality rate of patients with colorectal cancer (CRC) remains as high as 40% (1). The development of metastases is the main cause of mortality. Approximately 60% of patients with CRC develop liver metastases, which are synchronous in 1/3 of cases and metachronous in 2/3. Complete resection of liver metastases is the only validated treatment allowing for a possible prolonged survival, or even cure (2). However, this type of treatment is only possible in 15 to 20% of patients. No formal resectability criteria have been defined and the indication for surgery is exclusively based on the possibility of complete resection. In particular, the number of liver metastases is not a limiting factor. Median survival is not influenced by the number of metastases resected, provided resection is complete (3, 4). In some cases, complex surgical procedures may be necessary, possibly associated with radiofrequency ablation (5). The local efficacy of radiofrequency ablation is estimated to be 90%, but the indications for this modality are also limited (number, size and site of metastases).

In the great majority of cases (80 to 90% of cases), no local treatment can be considered, especially in the presence of multiple liver metastases involving both lobes. In such cases, systemic chemotherapy is proposed, generally comprising of 5-fluorouracil (5FU)-leucovorin (LV), either alone (LV5FU2) or combined with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). These latter regimens have provided an increase in objective response rates and median survival (6). Despite the high objective response rates, the complete response rate generally does not exceed 10%.

It may, therefore, be justified to try to increase the complete morphological response rates to chemotherapy in patients with metastases confined to the liver, but considered to be unresectable. The initial objective of this study was to sequentially combine chemotherapy and radiofrequency sessions. There is no cross-resistance or cross-toxicity between these two techniques and a synergistic action was even suggested experimentally in a study evaluating the impact of liposomal doxorubicin with and without radiofrequency on mammary tumour xenografts in Fischer rats (7).

First-line chemotherapy was performed according to the high-dose FOLFIRI (HD-FOLFIRI) protocol (8). Radiological assessment was performed every four cycles to assess the feasibility of radiofrequency and surgery. The objective was to achieve morphological complete clearance of metastases.
Patients and Methods

Patients. This study included patients with histologically-documented colorectal adenocarcinoma with metastases confined to the liver but considered to be unresectable at a multidisciplinary consultation meeting by specialized oncologists, radiologists and surgeons. The primary tumour had to have been treated curatively or was considered to be secondarily resectable (in the case of synchronous liver metastases). The other inclusion criteria were as follows: no extrahepatic metastasis; age: 18 to 75 years, WHO performance index ≤2, UDP glucuronosyl transferase-1A1 (UGT1A1) 6/6 or 6/7 genotype; satisfactory haematological, hepatic and renal function: neutrophils ≥2.0×10⁹/l, platelets >100×10⁹/l, prothrombin time (PT) >70%, activated partial thromboplastin time (APTT) <1.5×control, creatinine <135 μmol/l or creatinine clearance ≥60 ml/min, AST aspartate and alanine transaminases ≤3×upper limit of normal (ULN), alkaline phosphatases <5×ULN, normal serum bilirubin, no cirrhosis, no biliary-gastrointestinal anastomosis, no contraindication to general anaesthesia, no previous chemotherapy in the metastatic setting. Patients were included after signing an informed consent form. The study was approved by the Ethics Committee (June 8th 2005, number CP 04/38) of the University Hospital of Lille (France), and sponsored by the University Hospital of Lille.

Pre-treatment assessment. The tumour evaluation comprised an abdominal computed tomodensitometry (CT)-scan, preferably spiral [or a magnetic resonance imaging (MRI)], as well as a thoracic CT-scan. Positron emission tomography (PET-scan) was recommended. A blood sample was collected before inclusion for evaluation of haematological and biochemical parameters, and the UGT1A1 status.

Treatment. Chemotherapy cycles comprised irinotecan at 260 mg/m² (220 mg/m² during the first cycle) by two-hour infusion in combination with leucovorin at 100 mg/m², then a bolus of 5-FU at 400 mg/m² over 10 minutes followed by continuous infusion of 5-FU at 2400 mg/m² over 46 h. Cycles were repeated every two weeks until tumour progression, limiting toxicity, or the patient’s refusal. In the case of complete tumour response to chemotherapy possibly combined with radiofrequency and/or surgery, an additional six chemotherapy cycles were recommended. In June 2006, following the results of the pivotal study of first-line bevacizumab (9), an amendment was made to the trial to allow the addition of bevacizumab to chemotherapy whenever it was considered that further local hepatic procedure could not be performed. Bevacizumab was administered at a dose of 5 mg/kg on day 1 of the cycle.

Radiofrequency ablation was considered after each tumour evaluation (every four cycles of chemotherapy). The interval between cycles of chemotherapy could then be increased to four weeks instead of two weeks. The indication for radiofrequency ablation was discussed at a multidisciplinary consultation meeting by specialized oncologists, radiologists and surgeons. Radiofrequency could be performed either percutaneously, or by laparotomy, possibly associated with surgical resection (tumorectomy, hepatectomy). This procedure was performed under general anaesthesia. Target metastases for radiofrequency ablation had to be ≤3 cm in diameter. A maximum of three metastases could be destroyed during a single session. Ultrasound was preferably used to guide percutaneous application of radiofrequency therapy. The tip of the needle electrode was positioned in the metastasis to be destroyed. The appearance of a hyperechoic zone was monitored ultrasonographically and, at the end of procedure, had to completely surround the tumour zone. The number of needle positions was left at the operator’s discretion, but had to be reported on the procedure form. Each needle position was used to deliver radiofrequency therapy for 12 to 20 minutes. Surgical procedures were left at the liver surgeon’s discretion, and aimed to achieve complete R0 resection. All patients were informed about the nature of the trial and signed an informed consent form.

Endpoints. Primary endpoint: The primary endpoint was the rate of complete clearance of metastases. Complete clearance was defined by the absence of visible tumour on imaging (CT-scan and/or MRI). Each complete clearance had to be confirmed after four weeks.

Secondary endpoints: Secondary endpoints were: radiofrequency rate, surgical resection rate, objective response rates to chemotherapy according to RECIST criteria (10), progression-free survival, overall survival, and safety.

Statistical analysis. The complete response rate to chemotherapy generally does not exceed 10%. The objective in this study was to exceed a complete response rate of 30%. In order to observe such a rate, by defining the lower limit of this rate at more than 10%, with an alpha risk of 5% (bilateral), and a power of 95%, 36 evaluable patients were required. By assuming that 10% of patients would not be evaluable, a total of 40 patients had to be included.

Results

Eighteen patients were included, from June 2005 to November 2007, all at the University Hospital of Lille. The trial was stopped before the planned term due to the insufficient recruitment. One patient was withdrawn from the trial after inclusion, following the discovery of lung metastases. This patient was nevertheless included in the final intention-to-treat analysis. Patients’ characteristics at baseline are presented in Table I.

The patients received a median of eight cycles of chemotherapy (range=4 to 12). A partial response to chemotherapy was obtained in eight patients (44%), with stable disease in six (33.3%) (disease control rate=77.3%), and progressive disease in four (22%). Local treatment was performed in six responding patients and complete clearance of tumour was obtained in all six (Figure 1). After a multidisciplinary meeting, the retained local treatment was always surgery, in combination with radiofrequency ablation in four cases. Percutaneous radiofrequency ablation was never performed alone, as surgery always appeared to be preferable due to the size of the metastases or their contact with vascular or biliary structures. Surgery consisted of metastasectomy in four patients, right hepatectomy in one patient, and right hepatectomy and left metastasectomy in three patients. Radiofrequency ablation was combined with surgery in four patients. Two surgical procedures were necessary in two patients, at intervals of seven and five months, respectively, during which chemotherapy was continued. Complete global clearance by chemotherapy and
local treatments was obtained in six patients (33.3% on intention-to-treat analysis). Chemotherapy was continued for a median of three months (range=2 to 4 months) in these patients, with addition of bevacizumab in three cases. Chemotherapy did not induce any grade 4 toxicity or deaths. Main toxicities are presented in Table II.

In December 2012, two patients were still alive and one patient was lost to follow-up. The median progression-free survival in the overall population was 15.3 months, and the overall survival was 33.7 months (Figure 2).

Discussion

The objective of this study was to determine whether the strategy of combining systemic chemotherapy, radiofrequency ablation and surgery is able to increase the complete clearance rate of liver metastases and increase survival. This trial had to be stopped before term due to insufficient recruitment. Only one of the participating centres actually included patients. However, this trial indicates the feasibility of the treatment strategy evaluated. The HD-FOLFIRI regimen was well-tolerated, with only five grade 3 toxicities. This trial was limited to patients with UGT1A1 6/6 or 6/7 genotype, which may help to reduce toxicity. The objective response rate was 44%, in line with the results obtained in other trials (11). The phase II randomized METHEP trial conducted in patients with unresectable liver metastases evaluated various induction
chemotherapy regimens: FOLFIRI, FOLFOX, HD-FOLFIRI (up to 360 mg/m$^2$ of irinotecan), FOLFOX7, and 5-FU-irinotecan-oxaliplatin-leucovorin (FOLFIRINOX) (12). After 4 cycles of treatment, in a population of 122 evaluable patients (about 30 per arm), the most promising regimens in terms of response rate were FOLFIRINOX (response rate 57%) and HD-FOLFIRI (response rate of 47%). Other phase II studies have evaluated the first-line HD-FOLFIRI regimen with objective response rates of 48 and 57% (8, 13). In the present study, complete clearance of metastases was obtained by surgery, possibly in combination with radiofrequency ablation, in 6 out of 18 patients (33.3%). This is a high complete clearance rate and was the primary objective of the trial. Note that this trial was conducted on all consecutive patients with unresectable liver metastases. On inclusion, the probability of surgical treatment was extremely low or even non-existent for many of these patients. The median number of metastases was seven with a maximum of 30 metastases. This trial was not designed to select patients in whom metastases could have become resectable following response to chemotherapy, but to include all patients with unresectable metastases. The survival results were also promising, with a progression-free survival median of 15.3 months and a median overall survival of 33.7 months. These are particularly favourable results bearing in mind that all but two of the patients in this study had synchronous metastases, which is generally associated with a poorer prognosis.

Currently, most patients with metastatic colorectal cancer receive chemotherapy plus a targeted-therapy (bevacizumab or cetuximab), with interesting rates secondary resection for metastases (14, 15). The use of HD-FOLFIRI may represent an alternative in patients not suitable for targeted-therapies, for instance with a tumoural KRAS mutation contraindicating the use of anti-epidermal growth factor receptor (EGFR) antibodies, or a cardiovascular disease contraindicating bevacizumab. Moreover, recent randomized trials assessing the place of anti-EGFR agents in first-line therapy yielded discouraging results in terms of overall survival, suggesting that these agents are more useful when used in subsequent therapy lines (16). Systematic use of bevacizumab is limited by the concerns regarding haemorrhagic complications during surgery.

The strategy evaluated in this trial differs from that adopted in the European organization for research and treatment of cancer (EORTC) CLOCC trial (17). The phase II randomized CLOCC trial was conducted in 119 patients with colorectal cancer and unresectable metastases confined to the liver. This trial compared FOLFOX chemotherapy alone to maximum ablation of metastases by surgical radiofrequency ablation followed by the same chemotherapy regimen. The combined treatment was significantly superior to chemotherapy-alone in terms of progression-free survival (16.8 vs. 9.9 months, $p=0.025$), but, surprisingly, not in terms of overall survival (62% vs. 57% at 30 months). The absence of any difference in overall survival might be explained by the longer-than-expected survival of those in the chemotherapy arm, but also by the insufficient follow-up. In any case, these results are similar to those obtained in our study, but by means of local treatment with surgical radiofrequency ablation in all patients randomized to the combined treatment arm, as radiofrequency was systematically performed before chemotherapy. This systematic approach may not be appropriate for all patients. Specifically, patients whose tumors are resistant to chemotherapy are probably not good candidates for local therapy, and an unnecessary radiofrequency ablation may be detrimental in their case. It seems more logical to primarily assess tumour chemosensitivity before considering a local hepatic treatment. In the present study, the strategy appears to be more pragmatic and, by starting with chemotherapy, allows for better selection of patients most likely to derive a benefit from local hepatic treatment. Furthermore, in the CLOCC trial, patients were selected and were required to have fewer than nine metastases, while no upper limit was defined in our study (one patient had 30 metastases). In the CLOCC study, 40% of the patients had three or fewer than three metastases, and we cannot exclude the fact that in some of these patients, metastases were initially resectable. The novelty of the strategy explored in the present study was the consideration of all patients for potent local therapy, whatever the number and the size of initially non-resectable liver metastases, but also secondarily to propose this local therapy, only after selection by chemotherapy. In this way, the assessed strategy appears to be more personalized.

This approach is possibly beneficial for only a few patients who in routine practice would currently undergo systemic chemotherapy alone, as a result of the initial tumour extent. In our series, one out of three patients was finally operated on. We hypothesized that combination of complete responses to chemotherapy with resection or destruction of remaining metastases is a way to improve survival. The objective was a radiological complete clearance of metastases, which may be sufficient to prolong survival. This strategy, which additionally avoids unnecessary local therapy in most patients, may represent the best investigational arm in a randomized trial comparing it to chemotherapy-alone.

However, this study failed to evaluate a sequential treatment strategy, alternating chemotherapy and percutaneous radiofrequency ablation. At multidisciplinary meetings, when local treatment was considered possible, the modality used was always surgery, possibly combined with radiofrequency ablation. This could be related to the investigators’ personal assessment, but also to the anatomical characteristics of the metastases. Moreover, when the study was designed (2004), radiofrequency ablation was considered to be very promising, but this method was subsequently disappointing by comparison to surgery (18).
This study provides additional arguments in favour of an active strategy for patients with unresectable liver metastases. These patients should be systematically and regularly reviewed by a specialized multi-disciplinary team, even when it initially appears highly unlikely that local treatment is possible. The option of exclusive palliative chemotherapy could therefore be inappropriate in some of these patients.

In conclusion, this phase-II trial on unselected patients with unresectable liver metastases from colorectal cancer suggests that a strategy combining chemotherapy, surgery and radiofrequency ablation should not be excluded too hastily, and it may actually provide a prolonged survival. This trial, nevertheless, had to be terminated before term due to insufficient recruitment.

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References


