Xelox (capecitabine plus oxaliplatin) as neoadjuvant chemotherapy of unresectable liver metastases in colorectal cancer patients

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Complete resection of liver metastasis may provide long term survival in patients with colorectal cancer. Increased number of studies on succesful resection after neoadjuvant chemotherapy with initially unresectable liver metastasis has been reported. We evaluated retrospectively the results of 35 patients with unresectable liver only metastases from colorectal cancer treated with capecitabine plus oxaliplatin combination (XELOX). Treatment consisted of IV oxaliplatin 130 mg/m2 day 1 and oral capecitabine 1000 mg/m2 day twice daily on days 1 to 14 followed by 7 days of rest repeated every 3 weeks. After chemotherapy, 13 (37, 2 %) patients showed partial clinical response. Among them, 7 patients were considered suitable for surgery but 2 patients refused the surgery. While one of 5 patients had unresectable disease at surgery, the remaining 4 patients (11, 4 %) had a complete resection. There was one postoperative mortality due to sepsis within 2 months after surgery. Our data suggests that XELOX regimen seems to be useful in unresectable liver only metastases from colorectal cancer because of its activity, feasibility and tolerability. Further studies of XELOX in combination with bevacizumab and/or cetuximab are warranted in this setting.

Key words: XELOX, colorectal cancer, liver metastases, capecitabine, oxaliplatin

Surgical resection of liver metastases from colorectal cancer is known to be associated with long term survival (1-5) but only 10-20 % of patients with isolated liver metastases are candidates for curative liver surgery (6). A number of studies have confirmed that neoadjuvant chemotherapy has successfully downstaged liver metastases and rendered some patients resectable who were initially unresectable (7-15).

In correlation with recent development in the chemotherapy of colorectal cancer, new combinations including oxaliplatin/5-FU/FA (9, 11), irinotecan/5-FU/FA (16), irinotekan/5FU/FA/oxaliplatin (13, 17) and irinotecan/5-FU/FA/intraarterial chemotherapy (14) has been recently evaluated as neoadjuvant setting in patients with unresectable liver metastases and 48-73 % of response rate and 29-43 % of resectability has been reported with these regimens.

It has been reported that the XELOX is a highly effective and well-tolerated regimen and capecitabine has strong potential to replace FU/LV as the optimal combination partner for oxaliplatin (18). Moreover, very recently, XELOX has been reported to be equivalent to infused 5-FU/oxaliplatin regimen in the first line chemotherapy of metastatic colorectal cancer in a phase III randomized trial (19).

This is the first report evaluating the XELOX regimen as neoadjuvant setting in colorectal cancer patients with unresectable liver metastases only.

Patients and methods

We retrospectively evaluated the file records of 35 patients with unresectable liver only metastases from colorectal cancer received capecitabine plus oxaliplatin combination (XELOX) between July 1998 and May 2006. The median age was 58 years (range 28-75) and 20 (25%) patients were female.

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Table 1. Characteristics of patients

Characteristics	n (%)	Response Rates (%)				Underwent resection (%)
		CR	PR	SD	PD	
No. of patients	35 (100)	0 (0)	13 (37,2)	8 (22.8)	14 (40)	4 (11.4)
ECOG performance status						
0	15(42.8)	0 (0)	6 (40)	5 (33.3)	4 (26.7)	3 (20)
1-2	20(57.1)	0 (0)	7 (35)	3 (15)	10 (50)	1 (5)
Primary tumor						
Colon	20(57.2)	0 (0)	6 (30)	4 (20)	10(50)	2 (10)
Rectum	15(42.8)	0 (0)	7 (46.6)	4 (26.7)	4 (26.7)	2 (13.3)
Metastases						
Synchronousy	28 (80)	0 (0)	10 (35.7)	7 (25)	11 (39.3)	2 (7.1)
Metachronous	7 (20)	0 (0)	3 (42.8)	1 (14.4)	3 (42.8)	2 (28.6)
Reasons for unresectability						
A	19 (54.3)	0 (0)	10 (52.6)	3 (15.7)	6 (31.5)	3 (15.7)
B	4 (11.4)	0 (0)	2 (50)	1 (25)	1 (25)	1 (25)
C	0	0 (0)	0	0	0	0 (0)
D	0	0 (0)	0	0	0	0 (0)
E	1 (2.86)	0 (0)	1 (100)	0	0	0 (0)
A+B	5 (14.3)	0 (0)	0	0	5 (100)	0 (0)
A+C	1 (2.86)	0 (0)	0	0	1 (100)	0 (0)
A+D	1 (2.86)	0 (0)	0	1 (100)	0	0 (0)
A+B+C	1 (2.86)	0 (0)	0	1 (100)	0	0 (0)
A+B+C+D	3 (8.6)	0 (0)	0	2 (66.6)	1 (33.4)	0 (0)

A – Number of metastases (>4), B – Size of metastases (diameter >5cm), C – Unfavorable location of metastases, D – Massive liver involvement (>70%), E – Invasion of intrahepatic vascular structures

The inclusions criteria were as follows: no evidence of metastases at other sites, Eastern Cooperative Oncology Group (ECOG) performance status <3, no previous chemotherapy for advanced disease, adjuvant chemotherapy or concurrent chemoradiotherapy finished at least 6 months before, adequate bone morrow (white blood cell count >3x109/l, platelets>100x109/l, hemoglobulin >10g/dl), liver (total bilirubin<2mg/dl, aspartate aminotransferase or alanine aminotransferase <3xupper limit of normal) and renal (blood urea nitrogen <30mg/dl, creatinine <1,5x upper limit of normal), no history of other malignancies and age 18-75 years.

Responses to treatment were evaluated after every 2 cycles by ultrasonography and/or computed tomography and/or magnetic resonance image according to WHO criteria (20). Responders were defined as complete response (CR, disappearance of assessable disease) or partial response (PR, reduction of more than 50% of the lesion of the two largest tumor diameter). Stable disease (SD) meant less than 25% increases in tumor size. Progressive disease (PD) was defined by an increase of more than 25 % in tumor size.

Disease unresectabilty was established for all patients by teams that included surgeons, oncologists and radiologist who are expert in this field. The criteria of unresectability were the number of metastases (>4), and/or their size (diameter >5cm) and/or their location in both lobes and/or the percentage of liver involvement and/or the invasion of intrahepatic vascular structures. Resectabilty of liver metastases after the chemotherapy was reconsidered periodically, along with the objective response to chemotherapy by the same teams and was attempted when technically possible and when potentially curative.

Treatment consisted of IV oxaliplatin 130 mg/m2 day 1 and oral capecitabine 1000 mg/m2 day twice daily on days 1 to 14 followed by 7 days of rest repeated every 3 weeks. The dose of capecitabine was adjusted for adverse events of grade 2 or higher intensity, according to the standard scheme described by Blum et al. (21). The dose of oxaliplatin was reduced for grade 3 vomiting, grade 3 or 4 thrombocytopenia or grade 4 neutropenia and for paresthesiae with pain or functional impairment persistent between cycles.

Statistical analysis

Progression-free survival (PFS) was calculated as the period from the start of neoadjuvant chemotherapy to the first observation of disease progression or death from any cause. The overall survival (OS) time was calculated as the period from the start of neoadjuvant chemotherapy until death from any cause or until the date of the last follow-up. Both progression-free and overall survival times were estimated by the Kaplan-Meier method. Survival curves were compared with the log-rank test. P values less than 0, 05 were accepted as significant.

Results

Characteristics of patients, response to neoadjuvant chemotherapy and resection rates are shown in table 1. Twenty-eight

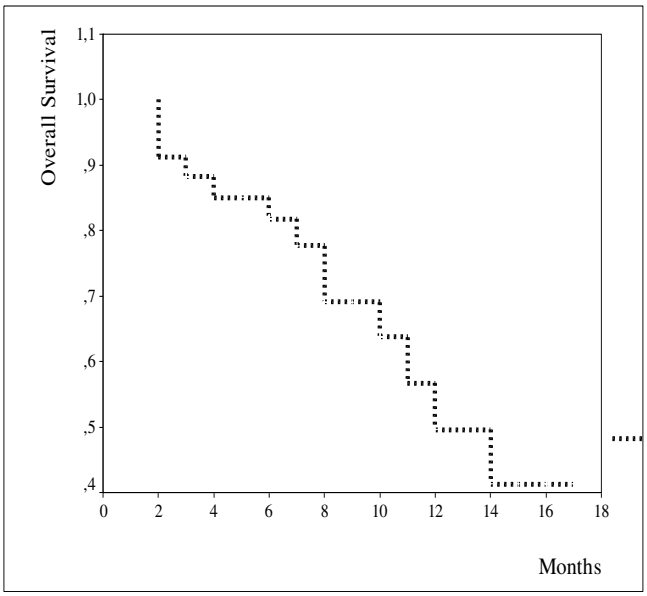

Figure 1. Overall survival of patients

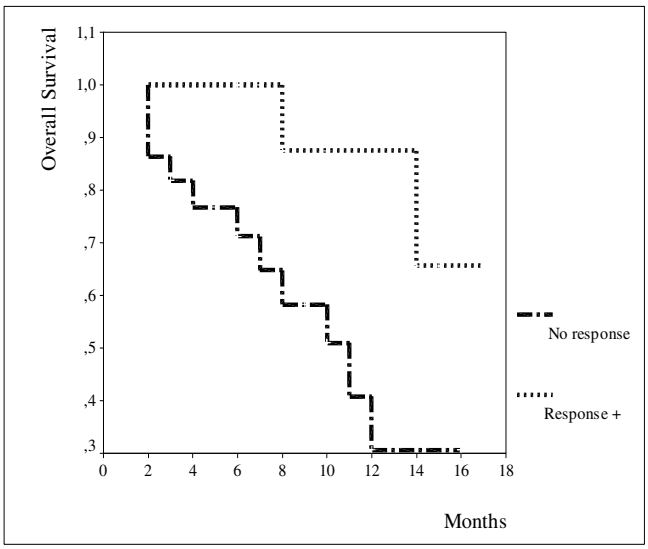

Figure 2. Overall survival according to response to neoadjuvant XELOX regimen

(%80) patients had synchronous and 7(%20) had metachronous liver metastases. Median overall survival was 12 months for all patients (95%: CI 8-16 months) (Figure 1).

A total of 123 cycles of chemotherapy were administered, with a median of 4 cycles per patient (range 2-9). The duration of chemotherapy ranged from 4, 5 to 8, 7 months (median 6, 7 months). A partial response was achieved in 13 (37, 2 %) patients and 8 (22, 8 %) patients had a SD more than 3 months. PFS was 11 months (95%: CI 9-14 months) for patients who had a response (PR). No complete response was observed. A total of 7 (20 %) patients with PR were considered suitable for surgery (five after six cycles of chemotherapy, 3 after 4 cycles of chemotherapy) after the complete evaluation by radiological imaging but one of them refused the surgery. Six patients who had a PR were not considered for surgery, because of lesion larger than >5 cm (1 patients) and miliary bilobar involvement (6 patients). The remaining 7 patients were considered to be suitable for metastasectomy, but 2 patients refused surgery and one of them had a radiofrequency ablation. After laparotomic evaluation, one of five patients considered suitable for surgery were found to have unresectable disease because of peritoneal involvement. The remaining 4 patients (11, 4 %) had a complete resection: 3 underwent multiple segmental resections and one had a right hepatectomy. There was one post-operative mortality due to sepsis within 2 months after surgery. Among patients with curative resection, one patient received six cycles of postoperative chemotherapy including irinotecan, bevacizumab and one patient received 4 cycles of oxaliplatin, xeloda and bevacizumab combination. The remaining one did not receive any additional chemotherapy. Three out of four patients (one died due to sepsis) with complete resection of liver metastases

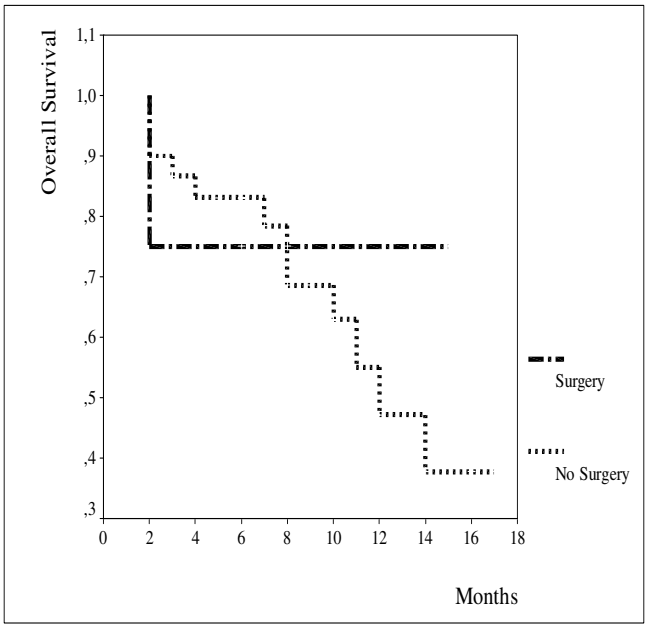

Figure 3. Overall survival of patients according to having complete resection or not

are still alive without any disease progression. Overall survival curves of patients according to response and complete resection are shown in figure 2 and 3, respectively. Patients who had an objective response (PR) after neoadjuvant chemotherapy had significantly higher median OS (15 months (95%: CI 13-17 months) vs. 10 months (95%: CI 7-15 months)) compared to the patients who did not respond to neoadjuvant

Table 2. Common toxicities

Toxicity	No. of patients (%)	
	All grades	Grade 3/4
Neutropenia	16(45.7)	6(17.1)
Febrile neutropenia	1(2.86)	1(2.86)
Neuropathy	10(28.6)	1(2.86)
Nausea/vomiting	13(37.1)	3(8.6)
Oral mucositis	10(28.6)	3(8.6)
Diarrhea	14(40)	6(17.1)

chemotherapy (p<0, 05). Median survival time has not been reached for patients underwent curative resection.

Adverse events are shown in table 2. Hematological toxicity (all grades) was reported by 16 (45.7 %) patients. Six (17.1%) patients experienced grade 3/4 neutropenia including one complicated with neutropenic fever. Gastrointestinal toxicities were acceptable: six (17.1%) patients experienced grade 3/4 diarrhea, but no patient required hospitalization. Grade 3/4 nausea and vomiting were reported in 3 (8.6 %) patients. In 3 (8.6%) patients, a dose reduction was required because of grade 4 neutropenia (one patient), grade 3 diarrhea (one patient) and grade 3 neuropathy (one patient).

Discussion

Hepatic resection of liver metastases is the only form of treatment that offers a chance of long term survival in colorectal cancer (8).Early experience with liver resection showed that some patients undergoing surgery were cured of their metastatic disease (22). Unfortunately, only 10-20 % of patients with liver metastases are suitable for curative liver surgery (6). Although few studies were reported before the era of new drugs (23), the advance that have been made in systemic chemotherapy have prompted reports of resections of initially unresectable liver metastases following chemotherapy (24). The low response rate of fluoropyrimidine-based regimens (10 % to 25 %) explains the lack of reports before the era of oxaliplatin and irinotecan. It was suggested that the survival of patients with initially unresectable liver metastases who undergo curative liver surgery after neoadjuvant chemotherapy is similar to the survival of patients with resectable liver metastases following chemotherapy (24).

Bismuth et al. (8) reported the first large retrospective analysis of patients with unresectable liver metastases. After the treatment of 330 patients with chronomodulated oxaliplatin/FU/LV, complete resection of liver metastases was obtained in 46 (14 %) patients with 40 % of 5-year survival rate. In two studies, FOLFOX-4 (11) and FOLFIRI (12) were used in patients with unresectable liver metastases and a response rate of 50 % was reported in both studies resulting in the complete resection of liver metastases in 33 % and 40 % of patients, respectively. Recently, four-drug combination (oxaliplatin, irinotecan, FU, FA) were used in two studies and higher response rates of 64 % (13) and 73 % (17) with 43 % and 35 % of complete resection rates were reported, respectively.

On the other hand, among studies designed for the palliative treatment of metastatic colorectal cancer, some reported results of patients with liver only metastases treated with more popular regimens including cetuximab (25, 26), gefitinib (27) and bevacizumab (28) in combination with oxaliplatin/FU/LV or irinotecan/FU/LV in their subgroup analysis and 43-78 % of response rate and 13-22 % of resectability were obtained.

In Sumpter's study (29), 47 patients with metastatic colorectal cancer were treated with XELOX and a 27, 6 % of response rate including 2, 1 % of CR and 13, 4 months median survival were reported. Our results with an overall response rate of 37, 2 %, a stable disease of 22, 8 % and a median OS of 12 months are similar to those reported by other authors with XELOX in metastatic colorectal cancer patients (18, 29-31). In contrast to these studies, however, there was no CR in our study. We treated our patients with curative intent and surgery was performed as soon as the tumor becomes resectable, because withholding surgery and continuing chemotherapy until best response may result in disappearance of all visible tumors and make patients inoperable. We can easily speculate that some of our patients underwent curative surgery would have CR if we continued chemotherapy in stead of performing surgery after PR. In other XELOX studies, however, patients were treated palliatively until best response.

Although there are many studies evaluating the role of different chemotherapy combinations in colorectal cancer patients with unresectable liver only metastases, only one study reported by Sumpter et al. (29) reported the results of a subgroup of 12 patients with liver only metastases after XELOX regimen and 5 patients (41, 6 %) had an objective response and 4 (33, 3 %) patients had a complete resection of liver metastases. However, the fact that one patient with progressive and one with stable disease had surgery in this study implies that some patients may have been resectable before neoadjuvant chemotherapy.

Our study is the first report evaluating XELOX regimen as neoadjuvant setting in unresectable liver only metastases from colorectal cancer patients. In our study, 7 patients were considered suitable for surgery but 2 refused the surgery. While one of 5 patients had unresectable disease at surgery, the remaining 4 patients (11, 4 %) had a complete resection. There was one postoperative mortality due to sepsis within 2 months after surgery. Although response rates found in our study are quite close to other studies investigated neoadjuvant chemotherapy in unresectable liver only metastases with current combinations including FOLFOX-4, FOLFIRI, a 11, 4 % of resectability rate seen in our study which would probably increase to 17, 1 % if we include patients refused surgery is somewhat less than 33 %-40% of resectability reached in other studies (11, 12). The initial assessment and criteria for unresectability are different between studies and most often poorly defined in many

published studies. While in one trial (17) patient inclusion criteria defined as technical non-resectability, in most other studies the definition of non-resectability was left to the evaluation of the local clinicians (24). If resectable liver metastases would have been declared erroneously nonresectable at first evaluation, the results could easily turn meaningless as mentioned for the study of Sumpter et al. (29). The relatively lower resectability rate of our study is probably related to the different unresectability criteria between the present and other studies rather than uneffectivity of XELOX. Despite retrospective nature of our study, unresectability was reviewed in all patients according to well established criteria mentioned in methods section by teams that included surgeons, oncologists and radiologist who are expert in this field. Standardization of guidelines for determining resectability will facilitate to compare the studies going to make in this area.

Some prognostic factors such as rectal site of primary tumor, number of >2 metastases and a tumor size exceeding 10 cm has been reported after resection of liver metastases in colorectal cancer patients (32-37). In our study, although statistical analysis is not possible because of small number of patients in each group, patients with good performance status, synchronous metastases and unresectability criteria due to number and size of metastases had higher resectabilty ratios in accordance to other studies (32-37) (Table 1).

XELOX regimen was generally well tolerated. In total, 17.1 % of patients experienced grade 3/4 adverse events, which seems better than other studies including infusional 5-FU plus irinotecan and/or oxaliplatin (11-13, 17). A dose reduction was required only in 8.6 % of patients, because of grade 3/4 toxicities. One patient died of sepsis probably related to the surgery.

In conclusion, XELOX regimen seems to be useful in unresectable liver only

metastases from colorectal cancer as neoadjuvant setting because of its activity, feasibility and tolerability. Moreover, XELOX is also a good combination candidate for implications of biologic agents such as bevacizumab and cetuximab to increase resectabilty rate in this setting. Further studies of XELOX in combination with bevacizumab and/or cetuximab are warranted in patients with unresectable liver only metastases for colorectal cancer.

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