Chemotherapy and target therapy as neo-adjuvant approach for initially unresectable colorectal liver metastases

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Abstract

Although surgery is the most effective treatment for liver metastases in colorectal cancer patients, only 15-20% of these patients are suitable for a radical surgical approach, and metastases recurrence may occur at follow up. In the last decade, the use of pre-operative chemotherapy in combination with new biological drugs has been introduced. We reviewed data of neo-adjuvant chemotherapy strategies aimed at increasing the resection rate of liver metastases in colorectal cancer patients who were initially considered unresectable.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the US with an annual incidence of 141,210 cases and 49,380 deaths.[1] Approximately 15-25% of CRC patients present liver metastases at diagnosis, and these lesions develop in another 50% at follow up.[2] Surgery is the most effective treatment for CRC metastases in terms of both progression-free survival (PFS) and overall survival (OS).[3] Indeed, the 5-year overall survival was 32-37% in highly selected patients following hepatic metastasectomy.[4-6] Nevertheless, only 15-20% of CRC patients with liver metastases are suitable for radical surgery and recurrence of metastases has been reported in up to 75% of treated patients.[7,8]

In the last decade, the outcome of these patients has been greatly improved due to the use of pre-operative chemotherapy in combination with new biological drugs,[9] advanced surgical techniques, and the changes in criteria for resectability. Indeed, such criteria are no longer based only on the number, size, margins of resection and location of hepatic lesions, but also on the achievement of R0 surgery with preservation of at least 30% liver function, with adequate vascular and biliary drainage.[10,11]

Current recommendations advise hepatic surgery only in those patients with a single lesion of less than 2 cm, and referral of patients to adjuvant chemotherapy after metastasectomy.[12] There are, therefore, another 3 clinical scenarios for the assessment of patients with CRC liver metastases: i) readily resectable liver metastases; ii) initially unresectable liver metastases; and iii) unresectable and never likely to be resectable liver metastases.[12] In the first case, neo-adjuvant chemotherapy is recommended to increase complete resection rate, to favor diminutive hepatectomies, to treat micrometastases, and to prolong relapse free survival (RFS). In the second situation, patients harbor some negative prognostic factors (*i.e.* multiple liver metastases >4, single metastasis >5 cm, synchronous disease presentation, lymph node positive, high tumor marker levels) so that they are selected to receive neo-adjuvant chemotherapy before surgery in order to convert unresectable to resectable liver metastases. In the last scenario, patients received only first-line palliative chemotherapy.

To date, it is widely recognized that CRC patients with initially unresectable liver metastases at diagnosis may be considered for surgery after adequate pre-operative treatment, achieving 10-year survival rates that are only slightly lower than those of patients with early resectable metastases.[13] There have been only a few studies investigating the role of biological agents in the neo-adjuvant treatment of CRC patients with metastases confined in the liver, and data have been indirectly extrapolated from those studies including patients with multiple metastases.

We reviewed data of neo-adjuvant chemotherapy strategies aimed at increasing the resection rate of liver metastases in those CRC patients initially considered unresectable.

Chemotherapy

The first studies conducted on metastatic CRC patients compared the oxaliplatin-based (FOLFOX) chemotherapy regimens with those containing irinotecan (FOLFIRI).[14,15] In a study of 220 unselected patients, a similar objective response rate (ORR) was observed: 56% *vs.* 54% with FOLFIRI and FOLFOX, respectively. However, FOLFIRI achieved a significantly higher rate of secondary surgery to remove metastases as compared to FOLFOX (22% *vs.* 9%; P=0.02), with a high-

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er R0 rate (13% *vs* 7%). Liver metastases were removed in all but one patient who underwent removal of lumbar aortic lymph node metastases.[14] Thirty patients had a single metastatic site, 3 had two sites, and one had three sites. These data were not confirmed in another study including patients with unresectable metastases confined in the liver.[15] Indeed, ORR was 41% and 35%, and R0 5.1% and 4.4% following FOLFIRI and FOLFOX, respectively.

In a phase II study enrolling CRC patients with unresectable liver metastases, FOLFOX4 achieved a 60% ORR, with a curative resection rate of 40% and an OS of 26 months.[16] Similarly, the resection rate of hepatic metastases following FOLFIRI regimens was 30-40% in selected patients.[17,18,19]

Interesting data emerged from a study in which neo-adjuvant treatment with combination of 5-FU, oxaliplatin and irinotecan (FOLFOXIRI) was compared with FOLFIRI in 244 CRC patients with unresectable liver metastases.[20] The triple therapy achieved a higher ORR (66% *vs.* 41%, P=0.0002), a higher R0 resection rate of liver metastases (36% *vs.* 12%; P=0.017), and an increase in PFS (9.8 months *vs.* 6.9 months; HR 0.63, P=0.0006) and in OS (22.6 *vs.* 16.7 months, HR 0.70, P=0.032). No perioperative mortality was observed and morbidity was seen in 27% of cases; this, however, resolved without any sequelae.[21] This was the first study demonstrating the safety and efficacy of neo-adjuvant triple chemotherapy in these patients.

In addition, perioperative chemotherapy proved to be important in reducing disease recurrence as compared to surgery alone in patients undergoing liver metastasectomy. In the EORTC 40983 phase III study of neo-adjuvant chemotherapy in CRC patients with liver metastases (number of metastases ≤4), 364 patients were enrolled.[22] Overall, 182 patients received 6 doses of neo-adjuvant chemotherapy with FOLFOX4, then liver metastasectomy, and a further 6 doses of adjuvant FOLFOX4, while the remaining 182 patients only underwent surgery. Despite a similar surgical resection rate (83% *vs.* 84%), an increase in disease-free survival (DFS) was observed in patients receiving chemotherapy as compared to those treated with only surgery. Indeed, the increase in DFS was 7.3% (HR 0.79, P=0.058) in the overall population, 8.1% (HR 0.77, P=0.041) in patients eligible for treatment, and 9.2% (HR 0.73, P=0.025) in patients undergoing metastasectomy. However, the incidence of post-surgical complications was higher in the chemotherapy treated group (25% *vs.* 16%, P=0.04) whereas the perioperative mortality rate was less than 1% in both groups.

Target therapy

The introduction of new biological drugs, such as bevacizumab and cetuximab, further increased the benefit of chemotherapy in CRC patients with liver metastases, particularly in the patients subgroup with positive prognostic factors, *i.e.* K-RAS oncogene status.

Bevacizumab

Bevacizumab is a monoclonal antibody against the vascular endothelial growth factor. It is used in addition to chemotherapy, leading to an increase of overall survival, PFS, and overall response rate.[23-27] Furthermore, it increased the rate of both resectable liver metastases and the R0 resection.

Data from phase III trials suggest that bevacizumab does not increase secondary resection rates when added to standard chemotherapy, both for irinotecan-based and oxaliplatin-based therapy, although the number of resected patients receiving bevacizumab are too low to allow us to draw any firm conclusions.[25,27] The BEAT study enrolled 1914 patients with metastatic CRC to receive chemotherapy (29% FOLFOX, 26% FOLFIRI, 18% XELOX, 16% monotherapy) in combination with bevacizumab. In the patient subgroup with only liver metastases (704 patients), the rate of metastasectomy with curative intent was 15.2%, while R0 was achieved in 12.1%. Specifically, the rate of curative intent was 20% in patients treated with oxaliplatin and 14.3% in those treated with irinotecan, while the R0 was 15.4% *vs.* 11.7%, respectively. The 2-year overall survival was 89% in patients undergoing liver metastasectomy, 94% in R0 and 54% in all patients with liver metastases only.[28]

An analysis of 105 patients treated pre-operatively with oxaliplatin-based chemotherapy with or without bevacizumab demonstrated an advantage for monoclonal antibody addiction in terms of a reduction in the number of residual tumor cells (23% *vs.* 45%, P=0.02), but not in increasing complete pathological response rate (11.3% *vs.* 11.6%, P=0.59).[29] On the contrary, a larger retrospective study of 305 patients showed that bevacizumab therapy achieved a higher major pathological response rate when added to either oxaliplatin-based chemotherapy (54% *vs.* 32%) or irinotecan-based chemotherapy (29.6% *vs.* 25.7%).[30] However, bevacizumab did not result in a significant increase in the complete pathological response. Bevacizumab therapy has also been tested in association with the triple FOLFOXFIRI chemotherapy, achieving a 77% response rate and 100% control of disease in 57 treated patients.[31] To date, 43% of patients with liver metastases underwent surgery four weeks following discontinuation of bevacizumab without observing postoperative complications, such as bleeding, impaired wound healing and abnormal liver regeneration. At a follow up at 18.4 months, DFS was 13.1 months. The safety of bevacizumab was also corroborated in another study analyzing data of 186 patients.[32] Of these, 112 patients received pre-operative treatment with FOLFOX or FOLFIRI, either alone or in combination with bevacizumab (38% and 21%, respectively) while 74 patients underwent liver resection without pre-operative treatment. The group treated with chemotherapy did not show any significant increase in liver toxicity or an increase in postoperative morbidity and mortality. Interestingly, the subgroup of patients who received bevacizumab showed a similar post-surgical complication rate as those patients who did not receive it.[32] However, in order to reduce surgical morbidity, it is currently recommended to stop therapy with bevacizumab at least six weeks prior to surgery and to resume its use 28 days after.[28,33] Indeed, some studies showed that surgical complications were more frequent in patients who underwent surgery within eight weeks after bevacizumab treatment as compared to those who were operated later (65.5% *vs.* 30.4%).[34]

A retrospective analysis of two phase II studies[28,35] evaluated the effects of bevacizumab therapy on liver parenchyma and the impact on radiological response according to RECIST criteria.[36] In one study, 56 patients underwent neo-adjuvant chemotherapy with XELOX plus bevacizumab while in the other study 50 patients were treated with neo-adjuvant FOLFOX or XELOX. In both studies, patients underwent surgery for hepatic metastasectomy 2-5 weeks after the last course of chemotherapy. A reduction in the incidence of hepatic sinusoid dilation was observed in the group receiving bevacizumab (42.3% *vs.* 52.2%, P<0.05), as well as a reduction in both perisinusoidal fibrosis and hepatocellular necrosis. Therefore, bevacizumab therapy seems to reduce the typical hepatic toxicity of chemotherapy used as neo-adjuvant treatment for liver metastases. On the contrary, there was no significant difference in radiological responses according to RECIST criteria between patients treated with bevacizumab and those receiving chemotherapy alone, and the control of disease was achieved in 95% and 92% of patients, respectively. An additional retrospective analysis of the same two studies assessed the correlation between bevacizumab and the tumor regression grade (TRG) and how the TRG is associated with the overall survival and DFS.[37] Metastases of 100 patients were analyzed and the results showed an increase in pathological responses and a reduction in TRG in patients who received neo-adjuvant treat-

ment with bevacizumab (P=0.008). Major histological response was achieved in 38% and 10% of those treated with bevacizumab or chemotherapy alone, respectively, whilst no pathological response was observed in 34% and 66%, respectively (P<0.001). The difference in TRG was significantly associate with both overall survival (P=0.036) and DFS rates (P=0.020).

Two recent phase II studies (overall 87 patients) evaluated the efficacy of bevacizumab in combination with FOLFOX6 in patients with unresectable CRC liver metastases, achieving ORR of 30-70.5%, liver resection in 42.5-95.5% and R0 surgery in 25-86.3%.[38,39] Data from an ongoing trial on the SOLA (S1+leucoverin orally+oxaliplatin+bevacizumab) regimen found an overall response rate of 86.2%, with a 100% control of disease, while the curative intent surgery rate was 17.2%. The PFS was 12.5 months with a 100% overall survival at one year.[40] Finally, the recent BOXER study, involving 46 patients with only liver metastases treated with neo-adjuvant chemotherapy according to XELOX plus avastin regimen, showed a radiological objective response rate of 78%, a 40% conversion rate of non-resectable liver metastases, and a curative intent surgery rate of 17.7% with an R0 rate of 6.52%.[41]

In addition to chemotherapy, bevacizumab also proved to be important in reducing disease recurrence as compared to surgery alone in patients undergoing liver metastasectomy. Furthermore, a phase II study enrolled 56 patients with liver metastases only who were potentially curable through metastasectomy.[42] All patients received chemotherapy treatment with capecitabine and oxaliplatin in combination with bevacizumab for a total of 6 administrations. The overall response rate was 73.2%, a stable disease was detected in 21.4% of patients, and 93% patients underwent radical resection of hepatic metastases. Five weeks after surgery, patients resumed therapy with a further 6 cycles of XELOX plus bevacizumab. None of these patients showed an increase in bleeding complications during surgery or during the process of wound repair. Despite a short follow up of three months to assess the full regenerative capacity of the liver, data suggest that bevacizumab, in the perioperative setting with a 5-week interval between the last administration of chemotherapy and surgery, is a safe and effective approach with a good overall response rate.

Based on the findings described above, it appears that bevacizumab does not compromise the feasibility of secondary resection of metastatic disease; it is unclear, however, whether adding bevacizumab has the potential to improve on the resectability rates achieved with chemotherapy alone (Table 1).

Cetuximab

Cetuximab is a chimerical human-mouse monoclonal antibody against the Epidermal Growth Factor Receptor (EGFR), that is a member of the ErbB family tyrosine kinase receptors (HER), including her-2/Neu, EGFR3 and EGFR4.[43] It is relevant in CRC because expression or up regulation of the *EGFR*-gene occurs in 60-80% of cases.[44,45] Its natural ligands include the Alpha Growth Factor (AGF), the Epidermal Growth Factor (EGF), amphiregulin (AR) and epiregulin (ER). Cetuximab has been approved for the treatment of patients with metastatic CRC who express EGFR and wild-type (wt) K-RAS.[45] Although K-RAS-wt seems to be the determining factor for cetuximab sensitivity, over 65% of patients KRAS-wt for codons 12-13 do not

Table 1. Objective response rate, curative intent rate and R0 in initially colorectal unresectable liver metastases, treated with bevacizumab.

Trials	Phase study	Line of chemotherapy	Overall (n)	Liver metastases	Treatment	RR (%)	Curative intent rate (%)	Surgery R0 (%)
Van Cutsem E, *et al.*[28]	IV	I	1965	704	FOLFIRI+BV FOLFOX+BV	-- --	14.3 20.3	11.7 15.4
Blazer DG, *et al.*[30]	Retrospective	Neo-adjuvant	305	305	FOLFIRI/XELIRI+BV FOLFOX/XELOX+BV	40.7 62.9	88.85	89.83
Masi G, *et al.*[31]	II	I	57	30	FOLFOXIRI+BV	--	--	43
Wong R, *et al.*[41]	II	Neo-adjuvant	45	45	CAPOX+BV	78	17.7	6.52

RR, response rate; BV, bevacizumab.

Table 2. Cetuximab in the treatment of colorectal cancer: response and resectability.

Trials	Treatment	PTS	RR (%)	P	Surgery R0 (%)	P
CRYSTAL	Folfiri+Cmab *vs.* Folfiri	608 *vs.* 609	46.9 *vs.* 38.7	P=0.004	4.8 *vs.* 1.7 PTS with only liver metastases: 9.8 *vs.* 4.5	P=0.002 P=n.a.
	KRAS wt	348	57.3 *vs.* 39.7	P<0.0001	1.7 *vs.* 1.1	P=0.699
OPUS	Folfox+Cmab *vs.* Folfox	168 *vs.* 169	46 *vs.* 36	P=0.064	n.a.	n.a.
	KRAS wt	179	57.3 *vs.* 34	P=0.027	9.8 *vs.* 4.1	n.a.
CELIM	Folfox6+Cmab *vs.* Folfiri+Cmab	53 *vs.* 53	68 *vs.* 57	P=0.23	38 *vs.* 30	n.a.
	KRAS wt	70	70 *vs.* 41	P=0.008	n.a.	n.a.
POCHER	Cmab+CPT-11+FA+5-FU+L-OHP	43	79	n.a.	60	n.a.
	KRAS wt	30	n.a.	n.a.	n.a.	n.a.

PTS, patients; RR, response rate; Cmab, cetuximab; wt, wild-type; n.a., not available.

respond to treatment with anti-EGFR monoclonal antibodies.[46]

The role of cetuximab in neo-adjuvant chemotherapy for CRC with liver metastases has been analyzed in several studies (Table 2). In the CRYSTAL trial, cetuximab plus FOLFIRI increased the rate metastases resection and significantly increased the rate of R0 resection compared to FOLFIRI alone (4.8% *vs.* 1.7%, P=0.002).[47] The early tumor shrinkage at eight weeks of first-line treatment with cetuximab was associated with a better long-term outcome.[47] In detail, early tumor shrinkage was achieved more frequently in patients with K-RAS-wt tumors receiving FOLFIRI plus cetuximab, and it was associated with significantly improved PFS and OS.[48] In the OPUS trial, 169 patients received cetuximab plus FOLFOX-4 while 168 patients FOLFOX-4 alone.[49] Treatment was continued until disease progression or unacceptable toxicity. K-RAS mutation status was assessed in the subset of patients with assessable tumor samples (233 patients). The objective response rates (ORR) were 46% *vs.* 36% with cetuximab plus FOLFOX-4 and FOLFOX-4 alone, respectively. In patients with K-RAS wild-type tumors, the addition of cetuximab to FOLFOX-4 was associated with a clinically significant increased chance of response (ORR 61% *vs.* 37%, OR 2.54, P=0.011) and a lower risk of disease progression (HR <0.57, P=0.0163) compared with FOLFOX-4 alone. The R0 resection rate was more than doubled in patients with K-RAS wild-type tumors who received cetuximab plus FOLFOX-4 as compared to those receiving FOLFOX-4 alone (9.8% *vs.* 4.1%). On the contrary, R0 resection rates were similar in both treatment arms (1.9% *vs.* 2.1%) when tumors carried K-RAS mutations.[49]

The CELIM study (randomized phase II trial) examined the efficacy of cetuximab with either FOLFIRI or FOLFOX in a neoadjuvant setting of unresectable only liver metastases.[50] Non-resectability was defined as having 5 or more liver metastases or metastases that were viewed as technically non-resectable by the local liver surgeon and radiologist on the basis of inadequate future liver remnant, or one of the following criteria: infiltration of all hepatic liver veins; infiltration of both hepatic arteries or both portal vein branches. The EGFR was detected in 81 (73%) out of 110 patients and the KRAS-wt in 67 (71%) cases, including 64 with wt for both KRAS and BRAF. Overall, R0 resection was achieved in 36 (34%) out of 106 patients, including 20 (38%) of 53 in FOLFOX and 16 (30%) of 53 patients in FOLFIRI. R0 or R1 resection and/or radiofrequency-ablation have been carried out in 49 (46%) of 106 patients. R0 resections occurred in 19 of 48 patients (40%), considering as criteria for inclusion the presence of 5 or more liver metastases and in 16 of 57 patients (28%) with the criterion of technically unresectable metastases. A review of resectability, based on radiological images alone, was performed for 68 of 106 patients. Following review, 41 (60%) of 68 patients were judged to be resectable after chemotherapy compared with 22 (32%) of 68 patients at baseline before chemotherapy. This difference was statistically significant (P<0·0001) leading to an additional 19 (28%) of 68 patients considered to be resectable after treatment. In a regression analysis, the outcome of chemotherapy (confirmed response) had a statistically significant effect on change of resectability (P=0·039). However, in these exploratory analyses, the number of metastases, previous liver resection or technical unresectability of metastases did not significantly affect the changes in resectability status.[50]

In the POCHER study (phase II trial), 43 patients received weekly cetuximab at day 1 plus chronomodulated CPT-11, 5-FU, FA and L-OHP for 2-6 days every two weeks.[51] Partial remission was achieved in 79% of patients, a stable disease in 11.6%, while 4 patients were excluded because of toxicity. The macroscopic total resection of liver metastases was achieved in 27 (63%) patients; further data are provided in Table 2.

In summary, the role of cetuximab in neoadjuvant treatment for CRC liver metastases is limited to patients with K-RAS wt status; it should be avoided in those patients with K-RAS mutations.

Conclusions

The use of systemic therapy to down-stage unresectable liver metastases to achieve resectability offers a curative option with long-term outcomes similar to those achieved with primary resection. Therefore, secondary resection is a valid treatment goal for certain patients with initially unresectable liver metastases and an important end point for future clinical trials.

Hepatic surgery alone is recommended only for those patients with a single lesion less than 2 cm, adding adjuvant chemotherapy following metastasectomy.[12] Indeed, benefit in terms of both PFS and OS with such an approach was observed.[52,53] Even though resectable patients have a good prognosis, perioperative chemotherapy is recommended to increase R0 rate, reduce hepatectomy size, treat micro-metastases, and prolong RFS.[12,22,42]

Patients with initially unresectable liver metastases that receive available first-line treatment options may show an increase in secondary resection rates. Because response rates correlate with secondary resection rates, aggressive approaches that increase the likelihood of pre-operative response seem to be opportune. Identification of the most effective and tolerable treatment for liver metastases in colorectal cancer is an important goal in oncology. Although surgery remains central to the therapeutic approach, the use of chemotherapy drugs and biological agents in the pre-operative setting helps to reduce liver metastases size, ensuring surgical resectability and the control of micrometastatic disease. The increased rate of patients who are candidates for hepatic metastasectomy after neoadjuvant treatment leads, in turn, to an improved prognosis. Both the currently available biological drugs combined with either FOLFOX or FOLFIRI chemotherapies are effective in the treatment of liver metastases with a low perioperative toxicity profile. The interesting results in terms of both *curative intent* surgery and R0 rates achieved with the combination of monoclonal therapy with FOLFOXIRI triple chemotherapy deserves further investigation. Further studies are needed to define the gold standard in first-line treatment in CRC patients with unresectable liver metastases only, although this strategy may no longer ignore the molecular profile of the single tumor and the performance status of the patient.

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