Assessment of Tumor Response and Resection Rates in Unresectable Colorectal Liver Metastases Following Neoadjuvant Chemotherapy with Cetuximab

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Abstract To investigate efficacy and safety of cetuximab combined with neo adjuvant chemotherapy regimen in patients with unresectable colorectal liver. This was a prospective trial with rate of Ro liver metastases resection as primary end point. Between January 2010 and December 2014, 46 patients with unresectable liver metastases from colon or rectum were enrolled. Patients received Cetuximab along with neoadjuvant chemotherapy where 34 (74 %) and 12 (26 %) patients received FOLFOX and FOLFIRI, respectively. They were assessed for response after 2–3 cycles by CT scan. Patients with resectable disease were offered liver surgery within 3–6 weeks of the last treatment cycle. The primary end point was resection rate of liver metastases, which was evaluated in all patients. Secondary end points were response rate according to Response evaluation criteria in solid tumors

(RECIST) criteria, perioperative morbidity and mortality. An objective response was observed in 28 (60.9 %) patients. Seven (15.2 %) patients were reported radiologically to have a complete response (CR); 21 (45.7 %) patients had radiological partial response (PR). An additional 12 patients (26.1 %) demonstrated stable disease (SD) and only six patients (13.0 %) had disease progression (PD). Microscopically complete resections (R0 resection) was performed in all 28 patients (60.9 %). The most frequent toxicities were skin rash and diarrhoea. There was no operative mortality. Chemotherapy with cetuximab yields high response rates compared with historical controls, and leads to significantly increased resectability. Complete resection of previously unresectable colorectal liver metastases can be performed with minimal morbidity and mortality. This therapeutic strategy involves a multimodal approach.

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Introduction

Colorectal carcinoma is one of the most common causes of cancer-related mortalities in both India and the world. Almost half the patients with colorectal cancer will eventually develop liver metastases during the natural course of the disease [1]. The liver is a frequent site of colorectal metastases, and 15 to 25 % of patients have liver metastases at diagnosis. In addition, 50 to 60 % of patients with localized disease at diagnosis eventually develop metastatic disease [2]. Historically, the median survival of patients with metastatic colorectal cancer treated with palliative care is approximately 6 to 12 months [3].

Surgical management of hepatic metastases of colorectal cancer has now become standard of treatment. But only a

minority of patients (10–15 %) are considered candidates for resection with overall 5-year survival rates ranging between 25 and 40 %. Therefore, most colorectal hepatic metastases (an estimated 70–80 %) on presentation are unresectable [4, 5].

It was first reported in 1996 by Bismuth et al. that preoperative chemotherapy, using oxaliplatin plus 5-fluorouracil (5-FU) and leucovorin [LV], enabled initially unresectable colorectal liver metastasis (CRLM) patients to gain the chance of undergoing liver resection with an improved 5-year OS of 40 % [6].

Neo adjuvant chemotherapy is currently accepted as the way forward for improving survival in patients with initially unresectable CRLM. Standard combination chemotherapy regimens comprising 5-fluorouracil (5-FU) plus leucovorin [LV] in combination with irinotecan, typically FOLFIRI or oxaliplatin (FOLFOX) have been reported to facilitate the resection of 9–40 % of initially unresectable metastases, and a median survival of 15 to 20 months [7–9]. Although, intensified chemotherapy such as FOLFOXIRI (i.e., oxaliplatin, 5-FU/LV and irinotecan) has been shown to have high response and conversion rates (19 %); however, it has not been generally recommended thus far due to its considerable toxicity [10]. For patients with disease progression during preoperative chemotherapy predicts poor prognosis, for which a change to other alternative chemotherapy regimens is recommended [11].

New data emerging from randomized trials suggest that the addition of targeted agents and a third cytotoxic might be even more effective.

The immunoglobulin G1 monoclonal antibody against the epidermal growth factor receptor (EGFR), cetuximab is effective when used in combination with chemotherapy. It has a clear indication in second- and third-line treatment of metastatic colorectal cancer. It was recently investigated both as monotherapy and in combination with chemotherapy in the first-line setting.

The addition of cetuximab to doublet chemotherapy regimens such as FOLFIRI or FOLFOX has been shown to increase response rates (RR), and prolong progression-free survival (PFS) and overall survival (OS) times in the first-line treatment of patients with CRLM and KRAS wild-type tumours. In these trials, the resectability rate for liver metastases was improved by the addition of cetuximab to chemotherapy, when retrospectively evaluated [12, 13]. More patients with CRLM would be rendered resectable with effective preoperative therapy, as the addition of cetuximab to chemotherapy is feasible in first-line therapy, which has been confirmed in a randomized phase II multicentre study of cetuximab plus FOLFOX or cetuximab plus FOLFIRI in the neo-adjuvant treatment of nonresectable colorectal liver metastases confined to the liver (the CELIM study), response rates of 85

and 66 % were reported in the FOLFOX6 and FOLFIRI arms, respectively [14].

It is concluded that cetuximab when combined with first-line chemotherapy increases the possibility of resection for patients with initially unresectable liver without increasing surgical mortality or liver injury [15].

The CRYSTAL and OPUS randomised clinical trials demonstrated that adding cetuximab to first-line chemotherapy in patients with KRAS wild-type metastatic colorectal cancer (mCRC) significantly improved PFS compared with chemotherapy alone. They confirmed the benefit obtained across all efficacy end-points from adding cetuximab to first-line chemotherapy in patients with KRAS wild-type mCRC [16, 17].

Cetuximab combined with triple cytotoxic drug therapy is evaluated, for potential extra efficacy on response rates and clinical outcome. Definitive results from the preoperative chemotherapy for hepatic resection (POCHER) study revealed an RR of 79 % and a complete resection rate of 63 % achieved by FOLFOXIRI plus cetuximab [18].

KRAS encodes a small G protein that links ligand-dependent receptor activation to intracellular pathways of the EGFR signalling cascade. Mutation at key sites within the gene, commonly at codons 12 and 13, causes constitutive activation of KRAS-associated signalling. Evidence indicates that tumour KRAS mutation is associated with the inefficacy of cetuximab [19].

A recent meta-analysis based on the CRYSTAL and OPUS trials reported the updated clinical efficacy of cetuximab combination therapy according to KRAS and BRAF mutation status. This analysis confirmed that in KRAS wild-type patients, the addition of cetuximab in first-line treatment achieves a statistically significant improvement in response rates, progression free survival, and overall survival compared with chemotherapy alone. However, it also concluded that BRAF mutation status does not appear to be a strong predictive biomarker for the addition of cetuximab. BRAF is more likely to be a prognostic factor as the clinical outcome in BRAF mutant patients is worse than those with BRAF wild-type tumours in terms of RR, PFS and OS. Thus, BRAF testing is probably not essential when deciding whether cetuximab should be used [20].

The evaluation of tumour response to treatment is critical for managing patients with advanced cancer. Tumour response, partial and complete response, is the most common criterion used to evaluate the effect of treatment. Imaging and, in particular computed tomography (CT) scan is used to monitor chemotherapy according to the new guidelines for response evaluation (RECIST criteria) [21]. Complete response is usually defined as the disappearance of target lesions on imaging and is considered as a good indicator to evaluate the efficacy of chemotherapy. A potential drawback of neoadjuvant chemotherapy in metastatic colorectal cancer patients is missing the optimal timing of liver resection because of

complete response of liver tumours during chemotherapy. Studies show that there is a discrepancy between a complete response being seen on imaging and the complete clearance of cancer. Macroscopic residual disease was found during surgical exploration at the site of liver metastases that were considered to have disappeared on imaging. In addition, in patients with no obvious disease at surgery, microscopic cancer was observed in the resected specimen. Therefore, although complete response seen on imaging may be a useful criterion for evaluating the efficacy of chemotherapy, it does not mean the cure of cancer in most cases [22].

The technical problems for the surgeon are to identify the precise site of the liver needed to be resected and to achieve sufficient resection margin, since he cannot see or palpate any tumour or visualize it using intraoperative ultrasound. To avoid such an intractable condition, it is recommended that the evaluation of liver lesions be repeated every 2 months during preoperative chemotherapy and medical oncologists should refer patients to surgeons as soon as liver metastases are resectable before they have completely disappeared.

Despite advances in survival with chemotherapy, surgical resection of hepatic metastases is still considered the only curative option for patients with liver metastases. Liver resection should be reconsidered if the tumour shows response after chemotherapy. The current criteria focus on what should be left after hepatic resection. Previous criteria for resection, such as the size, location, number of intrahepatic metastases and the presence of bilobar or extra hepatic disease have largely abandoned. Nowadays, the definition of resectability includes a complete resection with tumor-free surgical margins (R0 resection), sparing at least two liver segments having an independent inflow outflow, and biliary drainage. The amount of the liver remnant after resection should not be less than 20 % and 30 % of the total liver volume in normal and cirrhotic patients, respectively [22, 23].

Historically, only 5–10 % of patients with colorectal liver metastases were resectable. Currently, with the advances in diagnostic methods and new therapies, resectability rates have increased [24]. Apart from conversional chemotherapy, portal vein embolization, two-stage resection, and tumor ablation are effective approaches to improve resectability for initially unresectable patients. Preserving at least 20 % of future liver remnant is a major obstacle when performing an extended hepatectomy for extensive liver metastases. In this situation, Portal vein embolization (PVE) can be helpful to induce hypertrophy of the contralateral liver to fulfill the minimal liver volume requirement. Even after preoperative chemotherapy or PVE, some patients cannot become eligible for complete CRLM resection through a single hepatectomy. PVE combined with a two-stage resection may be helpful in such circumstances [25]. However, for patients who cannot undergo liver resection because of extensive liver metastases and

inadequate remnant liver volume, RFA can play an important role when combined with liver resection [26].

EGFR is widely expressed in skin and EGFR inhibitors (EGFRIs) are characterized by cutaneous adverse effects. The most commonly reported adverse event associated with cetuximab treatment is an acneiform rash that is mostly mild-to moderate in severity and occurs in 70–80 % of patients treated with cetuximab. The rash is rarely dose- or treatment-limiting, and may diminish in intensity with continued exposure to cetuximab. Improvement may be seen after treatment with topical antibiotic preparations, topical steroids or topical retinoids. The rash is self-limiting and resolves fully after discontinuation of cetuximab treatment [27–29].

Data suggest that skin rash may serve as a surrogate marker of EGFR-targeted mAb efficacy. In several analyses, both the presence and intensity of skin toxicity predicted objective tumour response in patients treated with cetuximab or panitumumab in mCRC. In patients receiving cetuximab monotherapy for refractory mCRC, longer survival times were observed in patients with rash of any grade as compared with patients experiencing no rash ($p=0.02$) [16].

In the OPUS study, a correlation between response rate and skin toxicity was observed: 13 % of patients with no skin toxicity responded versus 42.2 % if G1, 53.2 % if G2, and 66.7 % if G3–4. In the phase III randomised Crystal Study, a slight benefit in terms of overall response rate and progression free survival Cetuximab was achieved in the combination arm; however, greater the skin toxicity higher the progression free survival [16, 17].

In the EPIC study and EVEREST study showed similar results. A correlation between grade of skin toxicity and outcome was reported. Better response rate, progression free survival and survival were achieved in the Cetuximab arm compared to classic schedule [30, 31].

These observations support the consensus that patients with mCRC receiving EGFRIs who develop skin rash should be treated for the rash while continuing EGFR-targeted mAbs, because these patients may derive the greatest clinical benefit from therapy.

Study

The aim of our prospective study was to determine the response rate and resection rate of patients with unresectable colorectal liver metastases following neoadjuvant chemotherapy with cetuximab. Assessment of extent of liver involvement and Functional liver volume reserve (FLVR) was performed by use of spiral computed tomography (CT), which had to be performed within 1 month of the beginning of treatment.

Eligibility Criteria

Inclusion Criteria

Patients were eligible for this prospective study if they had histologically confirmed adenocarcinoma of the colon or rectum, with metastatic liver disease unsuitable for resection as defined by a multidisciplinary team including surgical oncologists, radiologists and medical oncologists. Unresectability was defined as not able to achieve at least 30 % of Functional liver volume reserve (FLVR) as defined by CT volumetric analysis or not able to achieve R0 resection (minimum of 1 cm margin) due to close proximity to vessels. In addition, eligible patients were required to have the following characteristics: age 19 to 80 years; an Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2 ; adequate bone marrow reserve, renal and hepatic function.

The presence of KRAS mutations was determined by allele-specific real time polymerase chain reaction assays at a CLIA (Clinical Laboratory Improvement Amendments)-accredited lab. Only K-ras wild type patients were included in the study. The KRAS mutation detection was done by PCR amplification of exon 2 (codons 12 and 13) and exon 3 (codon 61) of the KRAS gene, using RQ PCR Kit.

Exclusion Criteria

Exclusion criteria were extrahepatic disease, concurrent malignancy, those with a previous malignancy within the last 5 years, prior chemotherapy treatment and serious or uncontrolled concurrent medical illness and peripheral neuropathy (CTC $>$ grade 1).

Written informed consent was required from all patients prior to study entry. The study was approved by an independent ethics committee.

Pre-treatment Evaluations

Prior to therapy, all patients were assessed by physical examination, routine hematology, Carcinoembryonic antigen (CEA) levels and biochemistry analyses. CT-scan of the abdomen was done to define the extent of liver disease. PET was done to rule out any extrahepatic metastasis.

Treatment Plan

Patients either received the standard FOLFOX6 or FOLFIRI regimen with Cetuximab. They received Cetuximab (400 mg/m² initial infusion on week 1, then 250 mg/m² weekly), then oxaliplatin (100 mg/m²) with FA (400 mg/m²) plus 5-FU (400 mg/m² bolus plus 2400 mg/m² as a 46-h continuous infusion) every 2 weeks (FOLFOX6), or irinotecan (180 mg/m²) with the 5-FU/FA regimen described (FOLFIRI).

Allocation to FOLFOX6 or FOLFIRI was based on medical oncologist preference because both regimen were considered equally effective as first line treatment of colorectal cancer. Subjective symptoms, physical examination results, performance status and all adverse reactions were recorded before each treatment cycle.

Treatment courses were repeated every 2 weeks for a total of six courses unless there was evidence of progressive disease.

Toxicity and Dose Modification Guidelines

Adverse reactions were evaluated according to the National Cancer Institute Common Toxicity Criteria. If patients experienced a grade four haematological or $\geq$ grade three non-haematological adverse events, the dose of chemotherapeutic drugs was reduced by 25 % for all subsequent doses. In addition, for persistent severe neurotoxicity, despite a 25 % dose reduction oxaliplatin was temporarily withdrawn, with maintenance of 5-FU/LV until recovery. Treatment was delayed for up to 2 weeks if the absolute neutrophil count was $<1500/\mu\text{L}$ or the platelet count was $<100,000/\mu\text{L}$. The grading of EGFR-associated skin rash was performed using modified grading system by Pérez-Soler [32].

Statistical Analyses

The primary end point was resection rate of liver metastases, which was evaluated in all patients. Secondary end points were response rate according to Response evaluation criteria in solid tumors (RECIST) criteria, perioperative morbidity and mortality.

Assessment of Response

Tumor size was measured after every 2–3 cycles by CT scan and response was evaluated according to RECIST criteria. All cases were discussed for eligibility for surgery by a multidisciplinary team including medical oncologists, radiologists and surgical oncologists. Patients with resectable disease were offered liver surgery within 3–6 weeks of the last treatment cycle. Patients who showed progression or no response were started on secondary chemotherapy.

Surgical Technique

An echocardiogram, ECG, functional liver volume assessment and a lung function test were performed preoperatively. Liver resection was performed 3 to 6 weeks after the last administration of chemotherapy, and all patients must have recovered from any severe side effects of chemotherapy.

Curative liver resection was obligatory, which included the resection of all liver metastases with a negative margin.

Frozen section and intraoperative ultrasound were used if necessary. Ablative techniques were followed in addition to surgery.

Results

Patient Demographics

Patients were enrolled between January 2009 and December 2014. Forty-six patients with colorectal cancer and unresectable liver metastases were included into this prospective, non-randomized trial. Selected baseline demographics and disease characteristics are shown in Table 1. The enrolled patients had a median age of 57 (range 25–72) years.

All patients received neoadjuvant chemotherapy with Cetuximab with 34 (74 %) and 12 (26 %) patients receiving FOLFOX and FOLFIRI, respectively.

Response to Chemotherapy

Tumor response was evaluated in all 46 patients after 4 and 6 cycles of chemotherapy.

An objective response was observed in 28 (60.8 %) patients (Table 2). Seven (15.2 %) patients were reported radiologically to have a complete response (CR); 21 (45.7 %) patients had radiological confirmed partial response (PR). An additional 11 patients (26.1 %) demonstrated stable disease (SD) and six patients (13.0 %) had disease progression (PD).

Table 1 Patients Demography

Parameter	No of patients	%
Study population	46	100
Median age, years	54 (25–72)	
Sex (female/male)	21/25	46 % / 54 %
ECOG score		
0	35	76 %
1	11	24 %
Primary tumour location		
Colon	27	59 %
Rectum	19	41 %
Hepatic metastasis: Number		
Solitary	12	26 %
Multiple	34	74 %
Hepatic metastasis: Location		
Right	19	41 %
Bilobar	26	57 %
Left	1	2 %
Hepatic metastasis: Size of largest lesion		
<5 cms	14	30 %
>5 cms	32	70 %

Table 2 Objective Response Rates

Efficacy measure	No. of patients (n=46)	%
Objective response		
Complete	7	15.2 %
Partial	21	45.7 %
Stable disease	12	26.1 %
Progressive disease	6	13.0 %

The median number of neo adjuvant chemotherapy cycles per patient was 4 (range 4–6). The median time from last course of chemotherapy to surgery was 4 weeks (range 3–6).

Liver Surgery, Pathology, Morbidity and Mortality

Fourteen patients needed PVE prior to surgery and underwent resection 4–6 weeks later. R0 resection was performed in 28 patients who showed objective response. Multi-segmentectomies were necessary in 12/28 (43 %) patients and 16/28 (68 %) patients underwent major hepatectomies. Intraoperative ultrasound was used to mark the metastatic site in a few patients. Perioperative blood transfusions were given to 13 (46 %) patients. Nine patient received radiofrequency ablation in addition to surgical resection. Twenty-five patients underwent single stage surgery, and only three needed staged procedure.

Of the seven (15.2 %) patients who were reported radiologically to have a complete response (CR); two was pathologically confirmed complete response and viable tumor cells were discovered during pathology in the other five patients.

Postoperative complications were observed in only one patient who developed anastamotic leak on POD 6 with septicemia. Patient was taken up for emergency diverting loop ileostomy and recovered. One patient experienced wound healing problems. There was no operative mortality and median duration of hospitalization was 9 (range 5 to 17) days. The median follow up is 14 months.

The main treatment toxicity was severe diarrhoea and neurotoxicity. Neutropenia was not common. Cetuximab was associated with typically acne-like skin rash in 64 % (18/28

Table 3 Grade III/IV toxicities

Adverse effects / Complications	FOLFOX6+Cetuximab (n=34)	FOLFIRI+Cetuximab (n=12)
Haematological toxicity	2	0
Febrile neutopenia	0	1
Gastrointestinal toxicity	2	2
Hepatic toxicity	1	0
Skin toxicity	7	2

patients) with objective response, with 22.2 % patients having grade III/IV skin toxicity. In patients with stable/progressive disease response was seen only in 11 % (2 patients) with no grade III/IV rashes (Table 3).

Discussion

The management of patients with unresectable colorectal liver metastases (CLM) who have a dismal overall survival remains a common clinical challenge. Approximately 80–90 % of patients with metastatic colorectal cancer (mCRC) referred to specialist centres have unresectable metastatic liver disease at presentation [4].

Multimodality comprehensive treatment is the best therapeutic strategy for these patients. However, the optimal pattern of multimodality therapy is still controversial. To date, resection of liver metastases is the only curative treatment option. Current practice for patients whose metastases who has the potential to be rendered resectable by conversion chemotherapy is to treat with the most effective chemotherapy regimen, coupled with the recommendation that surgery should be conducted as early as possible to minimize chemical damage to the liver.

This is the first study in India that tests the efficacy of cetuximab in addition to combination chemotherapy as first-line treatment for patients with unresectable colorectal liver metastases and uses the rate of R0 resection of liver metastases as main end point.

The study revealed that combination chemotherapy plus cetuximab resulted in high response rates, rapid tumour shrinkage with a 100 % R0 resection rate. The objective response rate was 60.9 % with a partial or complete response noticed in 45.7 % and 15.2 % of the patients, respectively. In addition a further 26.1 % of patients had stable disease.

Toxicity was acceptable. The main treatment toxicity was severe diarrhoea and neurotoxicity. Neutropenia was not common. Dose reduction due to toxicity did not compromise response rate, resection rate and time to surgery. Cetuximab was associated with typically acne-like skin rash in 43 % of patients in our study group. In the patients who showed objective response the frequency of rashes was higher and seen in 64 %, with 19.6 % patients having grade III/IV skin toxicity.

Advances in surgery including precise preoperative imaging and control of intraoperative bleeding have improved outcomes in the resection of colorectal liver metastases. A low rate of perioperative and postoperative complications were observed in the present study. Similarly, no cases of operative mortality were noted.

Neo adjuvant chemotherapy with Cetuximab has a number of potential benefits in patients with unresectable liver metastases. The decrease of tumor volume reduces the magnitude of liver resection whilst sparing normal hepatic tissue and

improving the R0 resection rate. A significant tumor response allows easier resection and good postoperative recovery. Additionally, the response or tolerability will help determine the optimal adjuvant therapy.

Conclusion

Cetuximab with combination chemotherapy provides high response rates that allowed complete resection in all patients. Patients who underwent successful surgical resection of their liver metastases can expect a prolonged survival. In addition, the chemotherapy regimens were well tolerated and low rates of complications, morbidity and mortality were observed. Given the ever increasing incidence of disease, this type of multidisciplinary management and collaboration is integral to the success and quality of life of the patient.

Response rate is an important marker for neoadjuvant therapy. The encouraging response rates produced with Cetuximab in combination with chemotherapy suggest the potential for optimization of neoadjuvant therapy. Although further studies are required to clarify its potential role, Cetuximab with neo adjuvant chemotherapy should be considered as a valid treatment option in patients with unresectable liver metastases in colorectal cancer.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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