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Original article

Title:
Early tumor response as a survival predictor in previously-treated patients receiving triplet hepatic artery infusion and intravenous cetuximab for unresectable liver metastases from wild-type KRAS colorectal cancer

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ABSTRACT:

Background: Early tumor shrinkage has been associated with improved survival in patients receiving cetuximab-based systemic chemotherapy for liver metastases from colorectal cancer (LM-CRC). We tested this hypothesis for previously-treated LM-CRC patients receiving cetuximab (500 mg/m²) and triplet hepatic artery infusion (HAI) within European trial OPTILIV.

Methods: Irinotecan (180 mg/m²), 5–Fluorouracil (2800 mg/m²), and Oxaliplatin (85 mg/m²) were given as chronomodulated or conventional delivery. Patients were retrospectively categorized as early-responders (complete or partial RECIST response after 3 courses) or non-early-responders (late or no response). Prognostic factors were determined using multivariate logistic or Cox regression models.

Results: Response was assessed in 57/64 registered patients (89%), who had previously received one to three prior systemic chemotherapy protocols. An early response occurred at 6 weeks in 16 patients (28%; 9 men, 7 women), aged 33-76 years, with a median of 12 LM (2-50), involving 5 segments (1-8). Ten patients had a late response, and 31 patients had no-response. Grade 3-4 fatigue selectively occurred in the non-early-responders (0% vs 26%; p = 0.024). Early tumor response was jointly predicted by chronomodulation - odds ratio, OR: 6.0 [1.2 – 29.8] (p = 0.029) - and LM diameter ≤ 57 mm - OR: 5.3 [1.1 – 25.0] (p = 0.033). Early tumor response predicted for both R0-R1 liver resection - OR: 11.8 [1.4 – 100.2] (p = 0.024) and overall survival - hazard ratio: 0.39 [0.17 – 0.88] (p = 0.023) in multivariate analyses.

Conclusions: Early tumor response on triplet HAI and systemic cetuximab predicted for complete macroscopic liver resection and prolonged survival for LM-CRC patients.
within a multicenter conversion-to-resection medico-surgical strategy. Confirmation is warranted for decision-making.

Protocol numbers

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KEY WORDS:

Early tumor response, colorectal cancer, liver metastases, hepatic artery infusion, triplet chemotherapy.

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INTRODUCTION

The addition of targeted therapy to standard chemotherapy regimens in the recent years has greatly improved the prognosis of metastatic colorectal cancer (mCRC), especially in patients with wild-type RAS[1, 2]. Cetuximab-based chemotherapy has achieved higher overall response rates, longer progression-free survival (PFS) and overall survival (OS) as compared with chemotherapy-only regimens for patients with mCRC in first-[3, 4], second-[5] and third-line treatments[6, 7]. The combination of cetuximab with oxaliplatin and/or irinotecan-based chemotherapy has further enabled curative intent liver resections with apparent survival improvements[8].

Achieving tumour shrinkage is an important goal of chemotherapy of LM-CRC, as it can translate into previously unforeseen surgical resections[9, 10]. Early tumor shrinkage could thus represent an important clinical objective for rapid symptoms relief, identification of best candidates for LM conversion-to-resection[11, 12] and ultimately overall survival (OS) improvement.

Retrospective analyses of randomized clinical trials have suggested a robust association between early tumor shrinkage by 20% or more and OS, independently of treatment arm[13, 14]. In contrast large increases in objective “best” response rates modestly translated into OS benefits for first line chemotherapy in patients with mCRC[15, 16]. Early tumor shrinkage could thus help guide and optimize medico-surgical treatment strategies with curative intent.

The present retrospective analysis evaluates for the first time the relevance of tumor response earliness on hepatic artery infusion (HAI) of combination chemotherapy for efficacy outcomes. The combination of triplet HAI and intravenous cetuximab achieved an exceptionally high efficacy in previously-treated patients with KRAS wt
metastatic colorectal cancer within European Phase II trial OPTILIV[17]. Objective response rate was similar to that reported for 1st line systemic chemotherapy, while 30% of the registered patients underwent successful conversion-to-resection of extensive liver metastases[17].

PATIENTS AND METHODS

OPTILIV methodology was recently reported[17] and it is summarized below.

Patients

After approval by the regulatory authorities in France, Belgium, Portugal and Italy, the patients were enrolled in nine centers from 5/2008 to 3/2012. The patients had histological or cytological proof of colorectal adenocarcinoma, with wild type exon 2 KRAS. Liver metastases (LM) resection with curative intent had to be deferred at medico-surgical multidisciplinary review meetings. All inclusion and non-inclusion requirements have been reported[17]. Trial inclusion required at least one of the following criteria: (a) less than 30% residual liver expected after resection, (b) malignant disease in contact with either 3 hepatic veins, both portal veins, or the retrohepatic vena cava, (c) documented progressive disease on imaging or doubling of serum levels of carcino-embryonic antigen (CEA) or CA19.9 over the prior 90 days or less. Up to three extra-hepatic resectable lesions of ≤ 10 mm, prior exposure to oxaliplatin, irinotecan, 5-FU and/or cetuximab, or prior surgery for LM were allowed.

Chemotherapy administration

All the patients had an implanted HAI catheter placed surgically or radiologically one week or more before chemotherapy onset. A chemotherapy treatment course
involved the intravenous administration of cetuximab (500 mg/m² over 2.30 h in the morning) followed with triplet HAI, combined with usual intravenous supportive medications. This association was repeated every two weeks. The triplet HAI involved irinotecan (180 mg/m²), oxaliplatin (85 mg/m²) and 5-fluorouracil (2800 mg/m²) administered into the hepatic artery catheter as a conventional or a chronomodulated delivery scheme according to institution experience. Courses were given every two weeks. For chronomodulated delivery, Irinotecan was administered on day 2 as a 6-h sinusoidal infusion from 2:00 to 8:00, with peak flow rate at 5:00, Oxaliplatin was given as sinusoidal daily infusions from 10:15 to 21:45, with peak delivery rate at 16:00 on days 2, 3 and 4, and 5-Fluorouracil was administered as sinusoidal daily infusions from 22:15 to 9:45, with peak delivery at 4:00, in alternation with oxaliplatin, on days 2, 3 and 4). This treatment scheme was automatically delivered using a programmable in time multichannel pump (Melodie®, Axon Cable, Montmirail, France) connected to the HAI port using a 20G Huber needle. Conventional treatment administration consisted of a 1-h constant rate infusion of Irinotecan, then a 2-h constant rate infusion of Oxaliplatin on day 1, followed with a 48-h flat infusion of 5-Fuorouracil. Treatment was delivered using the Alaris® Syringe Pump (San Diego, California, USA). To evaluate hepatic arterial supply and catheter function, all the patients underwent a contrast angiography before each treatment course. The same combination of cetuximab and triplet chemotherapy had to be administered intravenously in case of HAI discontinuation and also after liver metastases resection.

Assessments
All the patients had a thoraco-abdomino-pelvic computed tomography (CT) scan before inclusion and after every 3 courses until protocol withdrawal. Anti-tumor activity was assessed at each center according to RECIST 1.0 criteria[18] and consisted in the relative change in the sum of the largest diameters of the target liver lesions between baseline evaluation and the subsequent ones in the absence of new lesions. Maximum response was classified as complete (CR), partial (PR), stable disease (SD) or progressive disease (PD). Early tumor response was defined as the achievement of CR or PR after the first 3 courses, while late- responses were documented after 4 courses or more. The non-early-response group included patients with late response, stable disease, or progression as best response. The feasibility of liver resection was decided at systematic multidisciplinary evaluations after every 3 courses at each center.

Hepatectomies were undertaken whenever a complete macroscopic resection with curative intent was deemed possible. An estimated residual liver of less than 30% after curative intent surgery, and/or tight disease contact with liver main vessels that contra-indicated initial curative intent liver metastases resection were considered criteria for not undertaking surgery. Clinical and biological assessments were performed before each course and involved blood cell counts, renal and liver serum biochemistry and plasma carcinoembryonic antigen (CEA) and CA19.9. Performance status and adverse events were graded according to WHO and NCI-CTCAE v3.0 scales, respectively.

**Statistical design and analyses**
OPTILIV aimed to increase the rate of macroscopic complete resection (R0 + R1) from a historical control rate of 15% ($P_0=0.15$) on currently available systemic neoadjuvant chemotherapy up to 30% ($P_1=0.30$), with $\alpha=5\%$ and $\beta=20\%$, according to the exact single-stage Phase II design method. This required the inclusion of 48 assessable patients for the primary outcome. A 30\% rate of non-evaluable patients was expected for technical reasons such as arterial complications, which could lead to HAI withdrawal within the first two months. As a result, the inclusion of 64 patients was planned. Patient characteristics, toxicities, response and conversion-to-resection rates were compared according to response earliness using Fisher exact test or Pearson $\chi^2$-test. Progression free survival (PFS) and overall survival (OS) were computed using Kaplan-Meier method, and compared with Log Rank. PFS was defined as the time between inclusion and progression or relapse, OS from inclusion to last known to be alive or death; the cut-off date for follow-up was March 1st, 2016. Differences between groups were validated using Log-rank test.

Univariate analyses identified those among the 12 following factors (with their reference definition) possibly impacting on early response: delivery schedule (chronotherapy), number of metastases per patient ($\leq 10$), liver spread ($\leq 25\%$), prior LM surgery or radiofrequency (no), LM unilaterality (unilateral), largest LM diameter ($\leq 57$ mm, median), liver segments involved ($\leq 6$), age ($\leq 58$ years, median), sex (male), number of prior chemotherapy lines (one), WHO PS (0), and cetuximab dose intensity over 3 courses ($> 205$ mg/m$^2$/week).

Joint predictive factors of early response and conversion-to-resection were determined using binary logistic regression method. The impact of early response and other factors on survival was assessed by computing hazard ratio calculated with Cox proportional hazard ratio model. All analyses were performed with SPSS®.
v18.0 software (Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Fifty-seven of 64 patients (89%) registered in OPTILIV from 5/2008 to 3/2012 were assessed for response and eligible for early tumor response analysis (Figure A). Seven patients were not considered because of HAI catheter-related technical issues including implantation failure (3 patients) or early complete dysfunction (4 patients).

The study population included 37 males (64.9%) and 20 females (35.1%) aged from 33 to 75 years (Table A). All patients were previously treated with one to three systemic chemotherapy protocols. The majority of patients had extensive liver involvement with bilobar liver metastases (84.2%), a median of 10 LM (1 to 69) and 6 segments involved (1 to 8). The largest metastasis diameters ranged from 15 to 172 mm with a median of 57 mm. Patients received a total of 359 protocol courses, resulting in a median number of 6 courses per patient (2 to 20). Triplet chemotherapy was delivered as conventional delivery for 281 courses in 41 patients or as a chronomodulated infusion for 78 courses in 16 patients. The main cause of protocol discontinuation was catheter related-complications (62.5% of patients)[17].

An objective response was documented in 26 patients (45.6%), being an early response for 16 patients (28%). The 41 patients (72%) with non-early-response included 10 late-responders (18%) and 31 non-responders (54%). Median time from protocol treatment onset to the first response evaluation was 6.4 weeks (range, 4.3 - 10.6) for early responders and 6.1 weeks (range 3.9 - 15.9) for non-early responders
The characteristics of early-response and non-early-response groups only differed for the diameter of the largest LM (median, 37 mm vs 60 mm; p from univariate analysis = 0.022) (Table A). Late-responders differed from non-responders with regard to bilobar liver lesions (12.5% vs 60.4% of patients respectively, p=0.024). The initial characteristics of the early responders were otherwise similar to those of the late responders. Median duration of HAI, from the first to the last protocol treatment day was 12.8 weeks (range, 5.9 - 51.6) for early responders, and 11.3 weeks (range, 2.3 - 58.9) for non-early responders (p= 0.20). The median number of HAI courses given was 6 for both early (range, 3 to 11) and non-early responders, 6 (2 - 20) (p= 0.54).

Overall, the median relative dose intensities of chemotherapy were 82.3% for both cetuximab and irinotecan, 80% for oxaliplatin and 79% for 5-fluorouracil over 3 courses. There was no significant difference between early responders and non-early responders. The main grade 3-4 toxicities encountered were neutropenia, abdominal pain, leukopenia, fatigue and diarrhea (Table B). Grade 3-4 fatigue was documented in none of the early responders, as compared to 11/41 patients (26.8%) in the non-early-response group (p=0.024).

**Predictive factors of early tumor response**

The diameter of the largest LM was significantly associated with an early tumor response. Thus, an early response was achieved in 11.5% (3/26) of the patients with a largest LM diameter > 57 mm as compared to 41.9% (13/31) of those whose largest LM was ≤ 57 mm (univariate analysis, p=0.011). Both a largest LM diameter ≤ 57 mm (p = 0.033) and chronomodulated HAI delivery (p=0.029) were joint predictive
factors of an early response, with respective Hazard ratio (HR) of 5.3 [95% CL; 1.1 – 25.0] and 6.0 [95% CL; 1.2 – 29.8].

**Impact of early-response on complete macroscopic liver resection rate**

Seventeen patients (29.8%) underwent macroscopically complete LM resection, including single-stage hepatectomy (14 patients), two-stage (2 patients) or three-stage (one patient). Partial hepatectomy was associated with radiofrequency ablation for five patients and portal embolization for one patient. Liver surgery was performed after a median treatment duration of 5.3 months (range, 2.6 to 19.3), without any statistically significant difference according to early vs non-early response.

Seven of 16 early responders (43.8%) underwent R0-R1 liver surgery, including 5/5 on chronotherapy (100%) and 2/12 (16.7%) on conventional delivery. The other factors significantly associated with increased R0-R1 resection rates were a number of LM ≤ 10, and a single prior chemotherapy line. Joint positive predictors of R0-R1 resection included early tumor response (HR = 11.78, p= 0.024), > 10 LM (HR = 0.004, p = 0.001), a single prior chemotherapy protocol (HR = 20.8, p = 0.007) and an age < 58 years (HR = 10.95, p = 0.026), according to multivariate logistic regression analysis.

**Relevance of early-response for progression-free survival (PFS) and overall survival (OS)**

Median PFS was 2 months longer in early-responders as compared to the non-early responders - 11.6 months [95% CL, 5.4 -17.8] vs 9.3 [6.0 - 12.6] (Table C). However, early response was not identified as a statistically significant prognostic indicator of PFS according to both univariate and multivariate analyses.
Median OS was 14.9 months longer in the early-responders as compared to the non-early responders – 35.1 months [33.8 – 36.4] vs 20.2 [13.7 – 26.8] (p from Log Rank = 0.01, Figure B). Multivariate analysis confirmed early response as an independent predictive factor of OS (HR = 0.39; p=0.023), jointly with the following conditions: R0-R1 resection (HR=0.25; p=0.001), liver involvement ≤ 25% (HR=0.40; p=0.03), a single prior chemotherapy protocol (HR = 0.43, p=0.014), and age > 58 years (HR=0.41, p=0.02). No statistically significant effect was found for sex, primary tumor site (colon vs rectum), liver only disease, largest metastasis diameter, WHO PS, or acneiform rash (Figure C). Subgroup analysis further suggested the survival benefit resulting from an early response was strongly associated with chronomodulated delivery (Figure D).

DISCUSSION

OPTILIV is the first prospective multicenter trial worldwide involving the administration of the three major chemotherapy drugs against CRC (irinotecan, oxaliplatin and 5-fluorouracil) into the hepatic artery in order to convert-to-resection initially unresectable LM. Such liver-targeted chemotherapy modality aimed to achieving direct contact of drugs with the tumor cells into the liver, thereby enhancing tumor cell death and reducing the risk of hepatic relapse[19, 20]. This mechanism should thus both accelerate and increase magnitude of LM shrinkage[19]. A prior salvage study offered an initial proof of this therapeutic concept in 29 patients receiving chronomodulated HAI of irinotecan, 5-fluorouracil and oxaliplatin for unresectable liver metastases, following failure of a median of four prior systemic chemotherapy protocols[21]. OPTILIV further combined chronomodulated or conventional triplet HAI delivery with intravenous cetuximab in 64 patients with prior
exposure to one to three chemotherapy protocols for extensive LM from KRAS wt colorectal cancer[17].

Early-tumor shrinkage was proposed as a surrogate endpoint for predicting long-term outcome of patients on cetuximab-based systemic chemotherapy[13, 14]. Yet the time to first tumor assessment, the method and the cut-off of relative changes in tumor size remain unsettled. In recent years, clinical studies showed that the addition of targeted agents to chemotherapy could induce tumor necrosis without significant changes in tumor size[22, 23]. These findings made it difficult to define any clinically-relevant cut-off limit for tumor shrinkage. This was illustrated in our study as well, since nine patients underwent successful liver resection, despite no objective response being documented using conventional RECIST criteria. However, tumor size reduced by a median value of 18% (0 to -29%) in these patients. In the same way, no significant association was found here between overall best objective response and complete macroscopic liver resection. Recent retrospective studies[12, 13, 24, 25] have addressed this issue through considering early tumor shrinkage as a better indicator of more stringent efficacy outcomes. They defined early tumor response as a relative change of ≥ 20% in the sum of the largest diameters of target lesions at nearly 8 weeks compared to baseline. In this setting, Ye L.C. et al[11] and Douillard J.Y.[12] demonstrated that macroscopic liver resection was significantly associated with early tumor response on intravenous chemotherapy. In the present analysis, we determined both early and late responses according to RECIST criteria, qualifying early response as a PR or CR after three treatment courses. Early tumor response significantly predicted for conversion-to-resection on triplet HAI and iv cetuximab. Our study further emphasized the possible role of chronomodulated triplet HAI for maximizing the chances of an early response. Thus, chronotherapy
induced twice as many early responses as compared to conventional delivery (44% vs 22%), resulting in more R0-R1 resections (31% vs 5%), and a better overall survival. These data obtained in a limited yet multicenter patient sample support further prospective randomized evaluation.

Statistically significant longer PFS and OS have been reported in patients with early tumor shrinkage ≥ 20% as compared to those without early shrinkage in several studies[24-28]. Early response was here associated with a non-statistically significant PFS prolongation by 2 months as compared to non-early response. The median OS of early responders however was prolonged by 14.9 months, as compared to non-early responders, and by 23 months as compared to late responders. Such finding further suggests that the achievement of an early response could represent a critical therapeutic endpoint for future studies aiming at enhancing conversion-to-resection of metastatic disease and/or overall survival. In the current study, no grade 3-4 fatigue was observed among the early responders as compared to 27% in the non-early responders. This finding is consistent with reported improved tolerability and quality of life associated with an early response on intravenous chemotherapy[29]. However, we wish to emphasize the small sample size of our study and the high incidence of catheter-related issues, which however did not impair treatment efficacy or patient condition. From a clinical perspective, we feel that patients with initially unresectable liver metastases from CRC should be offered OPTILIV protocol at an early stage of the course of their metastatic liver disease. This would expectedly maximize their chances of an early tumor response, secondary R0-R1, and prolonged survival, while minimizing adverse events through short treatment duration.
In conclusion, the present study showed that an early tumor response predicted for increased LM conversion-to-surgery rate and prolonged survival in previously-treated patients receiving triplet hepatic artery infusion and systemic cetuximab for initially unresectable liver metastases from colorectal cancer. The concept of “early tumor response” on HAI therapies deserves further prospective trials, as it may help guide and optimize curative intent medico-surgical strategies in patients with liver metastases from colorectal or other malignancies.

AUTHORS’ DISCLOSURE

R. Adam has honoraria to disclose from Merck Serono, Sanofi Aventis, Amgen and a consulting or advisory role for Merck Serono and Sanofi Aventis.

P. Rougier has honoraria to disclose from Lilly for himself and from Ipsen, Sanofi, Celgene, Keocyt for immediate family member; he has to disclose a consulting or advisory role for Lilly (himself) and Sanofi (his institution) and research funding from Novartis (for his institution).

M. Ducreux has honoraria to disclose from Roche, Celgene, Merck Serono, Amgen, Novartis, Sanofi, Pfizer; he has to disclose grants from Roche, Chugai, Pfizer.

All remaining authors have declared no conflicts of interest.

REFERENCES


