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ORIGINAL ARTICLE

Surgical downstaging and neo-adjuvant therapy in metastatic colorectal carcinoma with irinotecan drug-eluting beads: a multi-institutional study

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Abstract

Background: Neoadjuvant chemotherapy for potentially resectable metastatic colorectal cancer (MCC) is becoming a more common treatment algorithm. The aim of the present study was to evaluate the efficacy of precision hepatic arterial Irinotecan therapy in unresectable MCC.

Methods: An open-label, multi-centre, multi-national single arm study of MCC patients, who received hepatic arterial irinotecan. Primary endpoints were safety, tolerance and metastatic tumour resection.

Results: Fifty-five patients with metastatic colorectal to the liver underwent a total of 90 hepatic arterial irinotecan treatments. The extent of liver involvement was <25% in 75% of the patients ($n = 41$), between 26 and 50% in 15% of the patients ($n = 11$) and >50% in 10% of the patients ($n = 24$). The median number of hepatic lesions was four (range 1–20), with a median total size of all target lesions of 9 cm (range 5.5–28 cm) with 50% of patients having bilobar tumour distribution. The median number of irinotecan treatments was two (range 1–5). The median treatment dose was 100 mg (range 100–200) with a median total hepatic treatment of 200 mg (range 200–650). The majority of treatments (86%) were performed as lobar infusion treatments, and 30% of patients were treated with concurrent simultaneous chemotherapy. Eleven (20%) patients demonstrated significant response and downstage of their disease or demonstrated stable disease without extra-hepatic disease progression allowing resection, ablation or resection and ablation. There were no post-operative deaths. Post-operative complications morbidity occurred in 18% of patients, with none of them hepatic related. Non-tumorous liver resected demonstrated no evidence of steatohepatitis from the irinotecan arterial infusion.

Conclusions: Hepatic arterial infusion irinotecan drug-eluting beads is safe and effective in pre-surgical therapy and helpful in evaluating the biology of metastatic colorectal cancer to the liver prior to planned hepatic resection.

Keywords

metastatic colon cancer, liver directed therapy, chemoembolization, irinotecan

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Introduction

Hepatic metastasis of colorectal cancer (MCC) is quite common occurring at some time in 23% of all of the 190 000 colorectal patients diagnosed each year.[1] While systemic chemotherapy can slow growth and even cause regression of hepatic metastases, long-term survival without local therapy is unlikely. Surgical resection of hepatic metastases continues to remain the optimal first-line treatment for hepatic colorectal metastases. Other local therapies that have been used are transarterial chemotherapy,

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ethanol injection, cryotherapy, radiofrequency ablation and microwave ablation. The role of hepatic transarterial therapy of hepatic colorectal metastases continues to evolve as the technology evolves and experience with this technique matures.[2] There have been recent reports of precision transarterial therapy in metastatic colorectal cancer with acceptable results.[3,4]

Patients presenting with initially unresectable metastatic colorectal metastasis either by a number of lesions or extrahepatic metastatic disease have the benefit of systemic 5 fluorouracil (FU)-based chemotherapy with a combination of oxaliplatin and/or irinotecan which offers a high rate of response (35–50%) and a longer median survival (15–20 months) vs. historical observation or 5 fluorouracil monotherapy alone.[5–7] However, patients who are refractory to 5FU-based systemic chemotherapy in combination with oxaliplatin rarely show a durable clinically relevant response rate for second or third line chemotherapy.[8] In a majority of patients, the most common site of refractory progression is within the liver. Thus, a minimally invasive hepatic-directed therapy that could potentially accentuate response rates as a monotherapy or in combination with systemic therapy is greatly needed.

Despite the advances in development of new cytotoxics and targeted biologics for the treatment of hepatic metastases from colorectal cancer, there is still interest in liver directed locoregional therapy to improve treatment response and potentially improve survival. Transarterial chemoembolization (TACE) is a locoregional therapy that is most widely used for the treatment of unresectable hepatocellar carcinoma (HCC).[9,10] It involves the periodic injection of a chemotherapeutic agent, mixed with an embolic material, into selected branches of the hepatic arteries feeding a liver tumour. A normal liver receives approximately 90% of its blood supply from the portal vein and 20% from branches of the hepatic artery.[11] In contrast, metastasis to the liver are hypervascular and receive their blood supply almost exclusively from the hepatic artery. The process of TACE involves the infusion of drugs such as irinotecan, doxorubicin, mitomycin C and cisplatin, with a viscous material (e.g. lipiodol) followed by embolization of the blood vessel with gelfoam, polyvinyl alcohol (PVA) particles or spherical embolic agents that will occlude arterial blood supply to the tumour. Therefore, two antitumoural mechanisms are acting together: the ischaemic insult related to the mechanical occlusion of the feeding arteries and the cytotoxic insult as a result of the targeted delivery of cytotoxic agents mixed with lipiodol, an oil that is specifically retained by neoplastic cells. A modification of this technique is the use of drug-eluting beads that combine the process of drug delivery and embolization in a single agent. The beads also allow for drug elution over days to weeks instead of a single infusion.[12,13] The expected advantage of TACE is that higher concentrations of the drug can be delivered to the tumour with decreased systemic exposure compared with systemic chemotherapy. Thus, the aim of this study was to evaluate the efficacy of precision hepatic arterial irinotecan therapy in unresectable MCC and evaluate the effectiveness of response to allow for surgical resection.

Materials and methods

An Institutional Review Board approved prospective multi-institutional open, non-controlled, repeat treatment registry was evaluated from January 2007 to October 2008 in which 50 patients presenting with liver dominant metastatic colon cancer (MCC) to the liver were treated with irinotecan drug-eluting beads.

Included were patients 8 years of age, of any race or gender, and had histological or radiological proof of MCC to the liver. Patients must also have had an ECOG performance status score of less than or equal to 2 with a life expectancy of greater than 3 months. Treatment of pre-menopausal women was permitted with an acceptable contraceptive. Exclusion to therapy was contraindication to angiographic and selective visceral catheterization, significant extrahepatic disease representing an eminent life-threatening outcome, greater than 75% of hepatic parenchymal involvement, severe liver dysfunction, pregnancy and severe cardiac co-morbidities. Only patients with liver dominant (defined as greater than 50% of the overall total disease burden) were considered for treatment.

Standard pre-therapy evaluation of patients with MCC included at least a three-phase computed tomography (CT) of the abdomen and pelvis and chest roentgenogram at least 1 month or less prior to treatment, with the use of positron emission tomography (PET) scanning depending on the institution and the availability of the technology. Prior systemic chemotherapy of any type and duration was allowed and was recorded.

Patients were followed for any treatment-related adverse experiences for 30 days after each treatment, and monitored for survival for 2 years. All adverse events from the chemotherapy were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 3.0. Follow-up assessments included a tri-phase CT scan of the liver within at least 1 to 2 months from the treatment completion with the evaluation of the enhancement pattern of the target lesion and tumour response rates measured according to RECIST, EASL,[14] and modified RECIST[15] criteria.

Hepatic angiogram

A diagnostic angiography was performed by the interventional radiologist and consisted of selective celiac and superior mesenteric arteriograms to evaluate the hepatic arterial anatomy. Defining the amount of liver disease was integral to defining both the number of treatments and the type of catheter position and therapy that would be performed. For finite numbers of lesions defined as less than four lesions (or <25% liver tumour burden), the treatment plan consisted of a minimum of two dosing schedules of at least 50 mg to 100 mg of irinotecan loaded in one to two DC/LC bead vials of either 100–300 microns, 300–500 microns or 500–700 microns. Treatments were scheduled at 3- to 4-week intervals and extended based on the toxicity. Most patients followed a plan of either two to three treatments based on the extent

of liver involvement with a repeat scan every three months from the initial first dose of treatment to evaluate response as well as planned re-treatment. For diffuse disease (25–50% liver tumor burden), a planned minimum of four doses was used again of 50–100 mg (depending on the extent of tumour burden and the extent of hepatic parenchyma reserve) irinotecan loaded into one – two DC/LC bead vials of the similar size as above with the plan for at least two treatments per lobe. The dosing schedule was again repeated every 3 to 4 weeks and extended if toxicity was seen. The patients with greater tumour burden were also followed with a planned repeat CT scan 3 months from the first dose to evaluate the tumour response.

Drug preparation

The saline suspension in the DC/LC bead microspheres (DEB; Biocompatibles UK, Surrey, UK) was removed and the beads were mixed with irinotecan solution at a dose of 50 mg per 2 ml at least 4 h before the procedure depending on the dose that was planned to be delivered. The mixture was stored for no longer than 14 days, and it was mixed with 5 ml of non-ionic contrast just prior to injection.

Resection or ablation

The decision to perform resection or radio frequency ablation (RFA) was determined at the discretion of the treating surgeon. In the patients undergoing hepatic resections, anatomic segmental liver resections were performed and classified as described by Couinaud.[16] Non-anatomical resections were performed when judged appropriate by the attending surgeon. For patients with disease that was felt to be unresectable because of the number, distribution, and/or location of the tumours, or because of patient co-morbid factors, ablation was performed. RFA was performed using intra-operative ultrasound guidance to ensure that at least a 1-cm ablation margin was achieved around the tumours.[17,18]

Post-operative complications and the length of hospital stay were prospectively evaluated. Complications were graded according to a standard five-point grading scale that has been utilized prospectively since June 2002.[19,20] All in-hospital and 90-day post-operative complications were evaluated with the highest severity level recorded. Peri-operative complications were defined as complications occurring within 30 days of the operation. RFA patients had one early CT (<1 month from RFA) to ensure RFA success and were then imaged per standard whereas resection patients were imaged per standard. Standard CT follow-up was utilized every 3 months for the first year and then every 6 months thereafter. Data were censored at the last recorded patient contact if an endpoint was not reached. Recurrence was also evaluated using serological markers and a PET scan. A recurrence was the re-occurrence of a viable tumour using radiological CT criteria of a vascular mass. In the event of subsequent hepatic therapy for recurrence of disease only the first procedure to evaluate response was used for the purposes of this study.

Chi-square, Student's *t*-test and Mann-Whitney's *U*-test for nominal, continuous and ordinal variables were used to evaluate the association of independent variables to surgical complications. Proportional hazards analysis was performed on all variables found significant by univariate analysis. Relative risk (RR) with 95% confidence intervals was calculated as a measure of association. Differences of $P < 0.05$ were considered significant. Statistical analysis was performed using JMP software (JMP; SAS Institute Inc., Cary, NC, USA).

Results

Patient and tumour characteristics

A total of 55 patients underwent 90 treatment sessions with the irinotecan drug-eluting beads. There were 25 (45%) women and 30 (55%) men in this study with a median age of 52 years (range 42–75). Past medical histories were significant for prior cardiac disease in seven patients, prior pulmonary disease in three patients, underlying diabetes in eight patients, prior alcohol abuse in five patients and tobacco abuse (median 60 pack years, range 30–120) in six patients. All of the study patients' past medical histories were negative for primary breast, carcinoid, renal, ovarian, melanoma, sarcoma and lung cancers. All patients had had their colon primary resected and 15 patients had undergone either prior anatomic hepatic lobectomy or RFA.

The extent of liver involvement was <25% in 75% of the patients ($n = 41$), between 26 and 50% in 15% of the patients ($n = 11$) and >50% in 10% of the patients ($n = 24$). The median number of hepatic lesions was four (range 1–20), with a median total size of all target lesions of 9 cm (range 5.5–28 cm) with 50% of patients having bilobar tumour distribution. The median number of irinotecan treatments was two (range 1–5). Median treatment dose was 100 mg (range 100 mg–200 mg), and the median total hepatic treatment dose was 200 mg (range 200–650), with 86% of treatments being performed in a lobar infusion treatment. Thirty per cent of patients were undergoing simultaneous systemic chemotherapy. Overall response rates on evaluable patients was acceptable, with data demonstrating that if response could be achieved after 6 months then this portended to a more durable response long term (Table 1).

Neo-adjuvant or downstage treatment

Eleven (20%) patients demonstrated either a significant response and downstaging of their disease or stable disease without

Table 1 Overall response rates on patients who were treated with irinotecan beads

	3 months	6 months	12 months	18 months
Complete response	6%	7%	6%	8%
Partial response	33%	35%	50%	83%
Stable disease	52%	54%	32%	0%
Progressive disease	9%	4%	12%	8%

Table 2 Clinical demographics of patients down staged or bridged to resection with irinotecan beads

Patient	Prior liver therapy	Cause for unresectablity and reason for initial bead treatment	No. of bead treatments	Operation after bead therapy
1	Lobectomy	Insufficient Remnant liver	2	Ablation
2	Lobectomy	Number and location	2	Ablation
3	Lobectomy	Location	1	Ablation
4	Ablation	Location	2	Ablation + Resection
5	Ablation	Number and location	2	Ablation + Resection
6	Ablation	Number and location	2	Atypical Resection
7	None	Lung mets	3	Lobectomy
8	None	Lung mets	3	Atypical Resection
9	None	Lung mets	3	Atypical Resection
10	None	Portal LN	3	Lobectomy
11	None	Portal LN	3	Lobectomy

LN, lymph nodes

extra-hepatic disease progression allowing resection, ablation or resection and ablation (Table 2).

Ten of the 11 patients were male; all were Caucasian, with a median age of 52 years, range 50–71. Four had non-insulin-dependent diabetes with only two having prior tobacco history, pack year ranging from 27 and 50 pack years, respectively. Three had had prior right hepatic lobectomy, and three had had prior open or percutaneous radiofrequency ablation at their initial metastatic presentation. At the time of referral for hepatic arterial therapy, median CEA level was 81.5 with a range of 2.6–488. All patients had multiple liver metastases, median of five and ranging from two to 15, with a median number of target lesions being three, range two to five. The most common location for metastasis was the right hepatic lobe. The single largest target lesion was a median of 2.6 with a range of 1.5–4.6 with the cumulative target lesions being a median of 3.5, a range of 2.6–10.1. Nine patients had less than 25% of the liver involved with the remaining two having 26–50% of the liver involvement. Five patients had extra-hepatic disease involving either the lung ($n = 3$) or periportal lymph node ($n = 2$). All patients had received prior systemic chemotherapy, including Folfox for a median duration of eight cycles, range 4–12 in nine patients, Folfiri in three patients with a median of six cycles, bevacuximab in 10 patients with a median duration of 12 cycles and five patients receiving capecitabine-based therapy for a median duration of 5 months. Three patients were treated with concurrent irinotecan and cetuximab-based therapy while undergoing their hepatic arterial irinotecan bead treatments. The remaining patients received irinotecan bead therapy alone.

The median number of irinotecan bead treatments in the operative group was three with a range of 1–3 treatments. Prior to treatment, all patients had a normal haemotological and hepatic synthetic function. All patients were treated with a single vial of beads loaded with 100 mg of irinotecan in a lobar infusion, either to the right or left hepatic artery. A variety of bead sizes were utilized with six treatments performed with 100- to 300-micron beads, seven treatments occurring with 300- to 500-micron beads and five treatments occurring with 500- to 700-micron beads. The total planned dose was given in all treatments except three in which 60%, 90% and 90% of the dose was administered prior to the development of complete stasis. After hepatic arterial bead treatment, the median length of stay was 23 h with a range of 23 h to 2 days. One patient suffered an adverse event consisting of post-embolic syndrome on day five, defined as nausea and emesis requiring outpatient intravenous hydration. Median observation time between last bead treatment and operation was 6 months with a range of 3 to 9 months to better confirm response to treatment, biology of the underlying disease and confirm stabilization or eradication of possible extrahepatic disease.

Six out of the 11 operative patients underwent hepatic resection which included three hepatic lobectomies and three atypical resections. Three patients underwent radiofrequency ablation alone and two patients underwent a combination of ablation and resection. There were no peri-operative mortalities, with two patients (18%) suffering complications during their peri-operative recovery. One included a post-operative biloma that required percutaneous drainage; the other was a minor wound infection that required oral antibiotics. The median length of stay of all 11 patients was 2 days with a range of 1–7 days.

Pathological assessment of the resected specimens showed minimal nonspecific portal chronic inflammation without evidence of fibrosis, or chemotherapy associated steatohepatitis (Fig. 1). The pathologic response also demonstrated of microbead clumping around the tumor capsule with minimal distribution in the non-tumourous liver. (Fig. 1) The overall pathological response rate in the resected specimens was 90%, range 30–90% degree of necrosis.

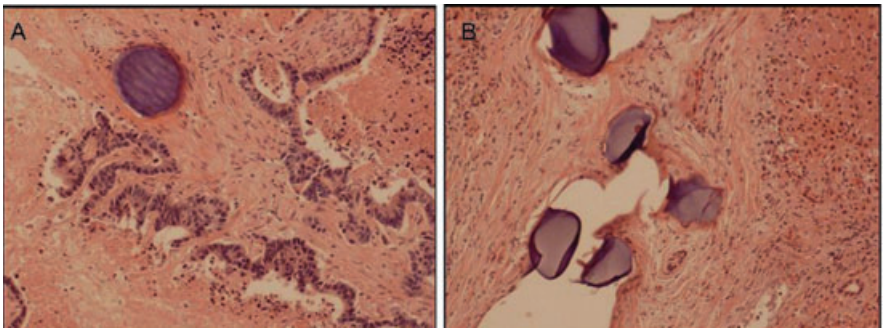

Figure 1 Pathological evaluation of a resected liver specimen with (A) embolic beads in tumour and (B) embolic beads at the interface between the tumour and the normal liver

After a median follow-up of 12 months after resection/ablation on all 11 patients treated, 9 patients had recurrence with a median disease free-interval of 9 months (range 6–18), with the most common (80%) being extrahepatic recurrence. Median overall survival after the operation was 12 months, with all patients currently alive.

Discussion

The multidisciplinary management of metastatic colorectal is becoming far more complex and far more collaborative in the optimal treatment of patients with metastatic colorectal cancer. 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.

Currently, the standard treatment for primarily resectable liver metastases from colorectal cancer is a curative metastatic resection. However, despite curative resection 67–85% of patients experience hepatic recurrence within 5 years and 65–72% of the patients die making multimodal therapies worth investigating. The neoadjuvant treatment of resectable colorectal cancer metastases is a relatively new concept with few studies reported to date. As such the long-term benefits are still under investigation. There are a number of potential benefits of neoadjuvant therapy of resectable CRC metastases such as:

- testing the chemoresponsiveness of patients in order to determine suitable adjuvant treatment post resection;
- neoadjuvant therapy may eliminate micrometastatic disease and dormant cancer cells in the liver and may decrease the risk of intra-operative dissemination of cells; and
- it may improve the rate of complete resection and decrease the amount of liver that needs to be removed at surgery.

In addition, some recent studies have suggested that response to neoadjuvant therapy may be an important prognostic factor enabling selection of good candidates for resection. There are, however, a number of potential drawbacks such as hepatic damage which may affect post-operative outcome, and delay of resection leading to disease progression.

The utilization of precision hepatic arterial irinotecan infusion as a monotherapy or in conjunction with current systemic chemotherapy opens up multiple opportunities in optimizing patients with high-risk metastatic colorectal cancer. Given the fact that response rates in second- and third-line systemic chemotherapeutic treatments are as low as 5–10% with significant added toxicity a more precise chemotherapeutic delivery to reduce these side-effects and to maximize response rates is a potential optimal treatment algorithm. A more precise delivery option is appealing as even patients who are responding to chemotherapy often have to stop because of ongoing neurological, hematological and gastrointestinal side effects.

In the management of metastatic colorectal cancer, hepatic-directed therapy is a well-established therapy ranging from hepatic arterial infusion pumps[21] to conventional TACE[22] to implantable infusaports.[23] The rationale and clinical success of hepatic arterial therapy is well established but can be plagued by significant adverse events including both the need for surgical intervention,[24] biliary sclerosis,[17] significant systemic exposure[23] and catheter dislodgement and misplacement leading to inadvertent aqueous extrahepatic infusion. LC/DC bead loaded with irinotecan has potential advantages that overcome all of the limitations of prior hepatic arterial-directed therapies. It is a more precision-directed device with minimal-to-no systemic side effects as has been reported in prior *in vitro* and *in vivo* studies.[13,25] The data presented here demonstrated no evidence of irinotecan systemic adverse events and all of our adverse events were related to the hepatic-directed therapy. All adverse events related to bead treatments, on review, appear to be technically related that can be improved with adjustments in bead technique.

The ability to administer effective high-dose cytotoxic irinotecan without inducing significant hepatic insufficiency, specifically steatohepatitis, is of utmost importance to hepatobiliary surgeons. Our data demonstrated no evidence of significant steatohepatitis even with the use of precision-based irinotecan predominantly related to point-directed chemotherapeutic effects that occur with the precision-based beads. The fact that metastatic colorectal cancer derives 95–100% of its blood supply from the arterial

system in comparison to the normal liver which derives 90% of its blood supply from the portal venous system allows for the point-directed chemotherapy to be administered without clinically significant non-tumorous hepatic toxicity, thus, making surgical resection and even aggressive surgical resection safe without the significant short-term and long-term toxicity that has been reported with intravenous irinotecan in the past.

This initial pilot evaluation confirms the activity of this device in the management of colorectal cancer liver metastasis. The present study also demonstrates that precision hepatic arterial irinotecan therapy is a safe and effective treatment option in the management of patients with metastatic colorectal. Hepatic arterial infusion irinotecan drug-eluting beads is an acceptable therapy for evaluating the overall metastatic biology of the metastatic colorectal cancer to the liver prior to planned hepatic resection.

Conflicts of interest

RCGM: Consultant Biocompatibles.

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