Transarterial Chemoembolization Using DEBIRI for Treatment of Hepatic Metastases from Colorectal Cancer

GOVINDARAJAN NARAYANAN, KATUZKA BARBERY, REKHA SUTHAR, GABRIELLA GUERRERO and GEETIKA ARORA

Department of Vascular and Interventional Radiology, Miller School of Medicine, University of Miami, Miami, FL, U.S.A.

Abstract. *Background/Aim: Dismal survival rates of metastatic colorectal cancer (mCRC) to the liver have been recorded. Transarterial chemoembolization (TACE) with irinotecan eluting beads (DEBIRI) may be a safe palliative treatment with fewer serious adverse effects (SAEs). We aimed to establish the safety and efficacy of DEBIRI TACE in the treatment of hepatic metastases from colorectal cancer (CRC). Patients and Methods: A retrospective analysis of DEBIRI TACE was performed. Response was assessed using the m-RECIST criteria. The Common Terminology Criteria for Adverse Events (CTCAE v3.0) were used to record toxicity. Survival was estimated using Kaplan Meier analysis. Results: Twenty-eight patients treated with 47 DEBIRI TACE procedures were followed from September 2008 until February 2012. Twenty-two had metastases from colonic cancer and six metastases from rectal cancer; three patients (15%) had complete response, six (30%) partial response, four (20%) stable disease and disease progression was recorded in seven (35%); computer tomography (CT) scans were unavailable for eight patients. AEs included gastrointestinal and acid-base disturbances, hypertension, fever, insomnia, chest pain, pruritus, and neutropenia; five patients did not present AEs. The median time from diagnosis of liver metastases to initial DEBIRI treatment was 19.6 months. The median follow-up was 6.9 months. The median overall survival from first treatment was 13.3 months (95% confidence interval=6.8-19.8 months). Conclusion: DEBIRI is a well-tolerated treatment option that can be used safely in the palliative treatment of hepatic metastases from CRC.*

Worldwide incidence of colorectal cancer (CRC) is approximately 400,000 patients. Sixty percent of these patients will develop liver metastases, with the liver being the second most common site of disease after lymph nodes and the most common site of refractory progression (1, 2). In approximately 35% of patients with CRC, metastases are confined to the liver (3). The survival rates for patients with liver metastases from CRC are improving, but 5-year survival is still only approximately 19.2% (4). Surgical resection of the affected portion of the liver offers the best chance for disease-free and overall survival (5, 6). Unfortunately, most patients present with disease that is not amenable to resection or have other contraindications to surgery. It is estimated that only 15-30% of patients are surgical candidates at initial disease presentation (7), the vast majority being treated with systemic chemotherapy and other locoregional therapies, including transarterial chemotherapy, radioembolisation, radiofrequency ablation, and microwave ablation(2). The recent availability of active chemotherapeutic agents has doubled the median overall survival for patients with metastatic colorectal cancer from 10 to 20 months (8).

The conventional first-line systemic chemotherapy for colorectal cancer usually includes FOLFOX [oxaliplatin, 5-fluorouracil and leucovorin] with or without bevacizumab, and can be interchanged with FOLFIRI [irinotecan, 5-fluorouracil and leucovorin], with or without bevacizumab, as second-line therapy. In patients without *K-RAS* mutations, third-line therapy typically involves the introduction of biological agents such as cetuximab to irinotecan-based regimens (9). Irinotecan belongs to a class of chemotherapy drugs known as topoisomerase inhibitors. It is derived from naturally-occurring plant alkaloids and is an active drug in the second-and third-line treatment of advanced CRC with systemic chemotherapy. These inhibitors are drugs that interfere with the action of topoisomerase enzymes controlling the structure of DNA necessary for replication.

Transarterial chemoembolization has been shown to deliver high-dose chemotherapy directly to target lesions within the liver with minimal systemic side-effects. This

Correspondence to: Govindarajan Narayanan, MD, Chief- Vascular & Interventional Radiology, Associate Professor of Clinical Radiology, University of Miami Miller School of Medicine, 1475 NW 12 avenue Miami Fl, U.S.A. 33136. E-mail: gnarayanan@med.miami.edu

Key Words: Transarterial chemoembolization, drug eluting beads with irinotecan, colorectal cancer.

technique, which has largely been used in the treatment of hepatocellular carcinoma, has expanded into treatment of liver-dominant metastatic disease. Recent data has suggested that TACE has the potential both to accentuate the palliation and potentially to improve quality of life in patients with CRC metastatic to the liver (1).

We present a retrospective analysis of the use of TACE using drug-eluting beads (DEBs) loaded with irinotecan in the treatment of CRC metastatic to the liver.

Patients and Methods

The study was a retrospective analysis of 28 patients who were treated with DEBIRI TACE from September 2008 to September 2011. Institutional review board approval was obtained prior to the study evaluation [#20070111].

Patient selection. TACE is performed at our institution under the following considerations: Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or less, total disease extent 70% or less of liver volume, total bilirubin of 3mg/dl or less. Patients with portal vein thrombosis and predominantly extrahepatic disease are not typically indicated for TACE.

Device preparation. LC bead microspheres (Biocompatibles UK Limited) were loaded with irinotecan in the pharmacy, and delivered to the interventional radiology angiosuite before the procedure. The DEBs were then aspirated from the vial into a Medallion syringe and contrast agent was added.

Procedure. Diagnostic angiography was performed by experienced interventional radiologists and consisted of selective celiac and superior mesenteric arteriograms to evaluate the hepatic arterial anatomy. Portal vein patency was established on the delayed phase. Once the vascular anatomy was evaluated, the major feeders to the lesions were identified. Selective lobar catheterization was then performed using a 4 French Glide Cobra or Berenstein catheters (Terumo Medical Corporation, Somerset, NJ). TACE was then performed under fluoroscopic guidance using a lobar approach until delivery of the product was achieved or when near stasis was reached.

If delivery was unilobar, 100 mg of irinotecan were loaded into one vial of 100-300 micron LC beads, and for bilobar delivery, one vial of 100-300 microns and a second vial of 300-500 micron LC beads were each loaded with 50 mg of irinotecan. The treatment plan consisted of a single TACE procedure per lobe with at least a four-week interval for a repeat TACE, if required. Patients were followed for toxicity; the interval between procedures was extended if toxicity was seen.

TACE was administered *via* the right hepatic artery in 21 procedures, the left hepatic artery in 11 procedures. One procedure was performed through the common hepatic artery into to the right lobe and one through the middle hepatic artery. Thirteen bilobar treatments were performed in a single treatment session. Nine treatments were split into the right hepatic artery and left hepatic artery in the same session; three were performed through the proper hepatic artery and one through the common hepatic artery. TACE was administered into two or more hepatic arteries safely in the same session in 10 patients.

Table I. *Periprocedural orders: University of Miami, USA*.

Periprocedural orders
1. Hydration on day -1, 0, 1 and 2
2. Dexamethasone 8 mg IV piggyback 6 h prior to chemotherapy
3. Dexamethasone 8 mg IV piggyback 30 min prior to procedure
4. Ondansetron 8 mg IV 30 min prior to chemotherapy
5. Ondansetron 8 mg IV 6 h s/p procedure
6. Cefazolin 1g IVPB 12 h and 6 h prior to chemotherapy
7. Cefazolin 1g IVPB Q 6 h while inpatient
8. Metronidazole 500 mg
9. Ranitidine 450 mg in 1 L of NS, to infuse over 10 h, followed by Zantac 450 mg in 1 L of D5W to infuse over 10 h by Zantac
10. 10 mg Morphine 30 min before TACE
11. 2-4 ml of intra-arterial lidocaine prior to LC Bead injection
12. 10 mg Morphine 6 h post-TACE
13. PCA with Dilaudid (hydromorphone) for a maximum of 1.2 mg per h

All DEBIRI injections were performed using a lobar approach, due to the limitations of conventional imaging in visualizing micrometastases. A super selective approach could potentially miss micrometastases within the liver. The standard hospital periprocedural management plan is listed in Table I.

Pain management. Irinotecan is a campothecin derivative and can cause pain and irritation on contact. We used a pain protocol that included 5 ml of intra-arterial lidocaine, injected slowly just before injecting on of DEBs along with 10 mg of morphine 30 min before the start of the procedure and another 10 mg of morphine while in the recovery area. Based on experience from four early treatments, where patients experienced Common Terminology Criteria for Adverse Events CTCAE version 3.0, grade 2 and grade 3 abdominal pain within the first 24-48 h post-injection of the DEBIRI, the pain protocol was modified to include intravenous hydromorphone at 1 mg increments every 5 min for a total of 4 mg while the DEBs were injected. These grade levels of abdominal pain were not experienced in other patients following the modification of the pain protocol.

Adverse event. Patients were allowed to have had prior systemic or targeted chemotherapy. The adverse effect profile was assessed based on patient symptoms following each procedure. Any treatment-related adverse effects experienced up to 30 days after each treatment were recorded. All adverse events and serious adverse events were recorded using the standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events CTCAE, version 3.0.

Imaging and tumor response. Prior to and one month post procedure, imaging with a triple-phase computed tomography scan or a contrast-enhanced magnetic resonance imaging was obtained after each treatment to assess for response. Response was assessed using the modified Response Evaluation Criteria in Solid Tumor (mRECIST); complete response was defined as disappearance of any intratumoral arterial enhancement in all target lesions; partial response as at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters; stable disease as any

Table II. *Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 3.0.*

Adverse event	Number of patients	Number of procedures	Grade 1	Grade 2	Grade 3
Fever	2	5	4	1	
Nausea	18	22	20	2	
Vomiting	12	13	11	2	
Abdominal pain	16	20	16	2	2
Insomnia	2	2	2		
Chest pain	2	2	1	1	
Epigastric	2	2	2		
Constipation	2	2	2		
Hypertension	3	3	1		2
Pruritus	1	1	1		
Hyponatremia	1	1	1		
Hypokalemia	1	1	1		
Hypomagnesemia	1	1	1		

cases that did not qualify for either partial response or progressive disease, and progressive disease as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions since the start of treatment (10). Patients underwent between one and five TACE procedures. The best tumor response was evaluated based on the best response patients achieved over their course of treatments.

Statistical analysis. Overall and progression-free survival analysis was performed using the Kaplan Meier estimator using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

Twenty-eight patients were treated with 47 TACE procedures using DEBIRI beads and were followed from September 2008 to February 2012. Twenty-two patients (78.5%) had colonic cancer metastases; six patients (21.5%) had metastases from rectal cancer. The patient age ranged from 43-82 years, with 25 patients (89%) being older than 50 years of age. The male to female ratio was 17:11. All patients underwent at least one TACE procedure, eleven had two, two had three and one patient had a total of five procedures.

Ninety-three percent of patients failed at least one line of chemotherapy. Six patients had undergone prior radiofrequency ablation treatment, two had had prior irreversible electroporation treatment, one patient had undergone TACE previously at an outside facility, and two patients had been given bevacizumab during the course of their systemic chemotherapy regimen with FOLFOX and/or FOLFIRI. Six patients had extrahepatic disease metastatic to the lungs, bones or peritoneum. Four patients had bilobar treatments in all sessions, 18 patients had unilobar treatments in all sessions and six had bilobar and unilobar treatments in different sessions. The median hospital stay was two days (range=1-7 days).

Table III. *Tumor response according to modified RECIST (11).*

Response	Number of patients	%*
Complete response	3	15
Partial response	6	30
Progression	7	35
Stable disease	4	20

*Calculated according to the patients for whom follow-up scans were available post-procedure.

Adverse events noted post-procedure are listed in Table II. Five (17.85%) patients did not present any adverse effects.

Laboratory values for 36 procedures were categorized according to the CTCAE criteria, version 3.0, to evaluate the toxicity and graphical presentations were used to describe the changes in the laboratory values at baseline, 24-48 h and 1-8 weeks. Regardless of the number of patients, all procedures were considered to describe changes in laboratory values with the intention to describe effect of irinotecan on liver function tests and white blood count (WBC).

One patient had grade 1 neutropenia at 24-48 h post-procedure. For 33 out of 34 procedures, patients had normal bilirubin levels prior to treatment. None of the bilirubin values exceeded the normal laboratory range at the 24-48 h time point.

Aspartate aminotransferase (AST) values exceeded the baseline grades in 20 out of 36 procedures 24-48 h post-treatment (Figure 1). AST values returned to the baseline level in 14 (70%) out of 20 procedures over the period of 1-8 weeks, one stayed at grade 1 and AST values were not available after five procedures during the period of 1-8 weeks. Alanine aminotransferase (ALT) values exceeded the baseline grades in 14 patients out of 35 procedures 24-48 h post-treatment (Figure 2). Six (42.9%) out of 14 returned to baseline ALT level over the period of 1-8 weeks and values were not available after the fifth procedure. In three procedures, the ALT values declined but did not reach baseline during the follow-up period. Alkaline phosphatase (ALP) values exceeded the baseline ALP grade in patients, in only three out of 34 procedures at 24-48 h post-treatment. Two out of three did not return to baseline over the period of 1-8 weeks and the ALP value was not available after one procedure.

Tumor response rates were evaluated using the mRECIST criteria and are listed in Table III. Complete response was seen in 3 (15%) patients. Six (30%) patients had partial response. Four (20%) patients had stable disease. Seven

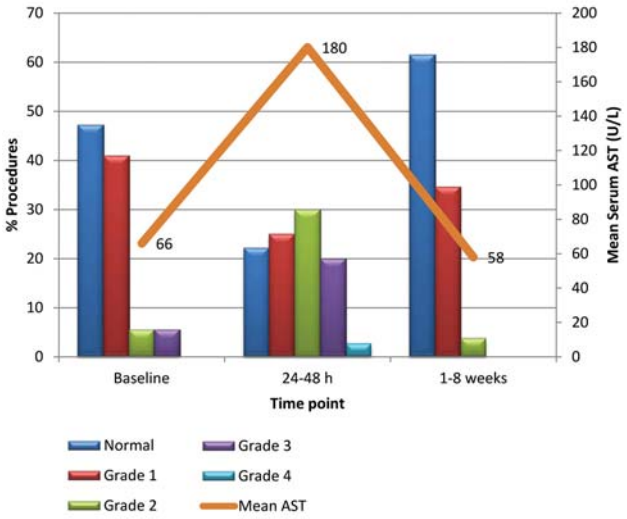

Figure 1. *Change in post-procedure mean serum aspartate aminotransferase (AST) levels with time. The bar graph depicts the distribution of AST elevation according to CTCAE grades at each time interval.*

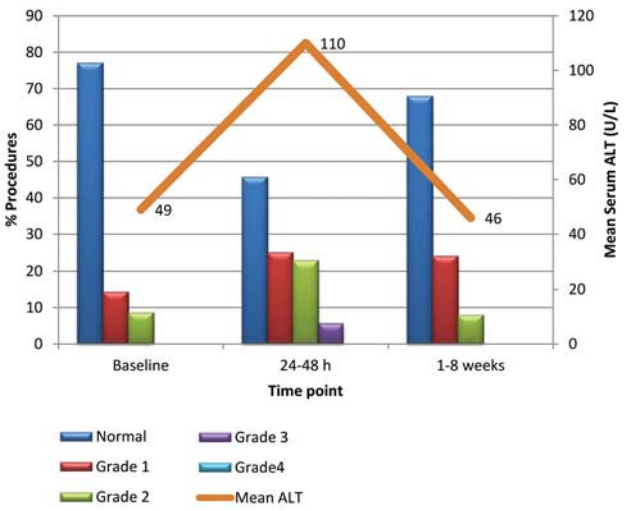

Figure 2. *Change in post-procedure mean serum alanine aminotransferase (ALT) levels with time. The bar graph depicts the distribution of ALT elevation according to CTCAE grades at each time interval.*

(35%) patients showed progression of disease. Eight patients did not have follow-up scans. Figures 3-5 show images prior and post-TACE procedure. The mean and median progression-free survival were 5.2 (95% CI=3.0-7.3) months and 4.0 (95% CI=3.4-4.6) months, respectively (Figure 6). The median follow-up was 6.9 months (range=0.2-35 months). The mean and median overall survival from the date of the first TACE procedure in our study were 14.1 (95% CI=9.5-18.6) months and 13.3 months (95% CI=6.8-19.8) months respectively (Figure 7). Six patients were alive at the time of writing the manuscript.

Discussion

Vogl *et al*. 2009 prospectively treated 463 patients with unresectable liver metastases of colorectal cancer that had previously not responded to systemic chemotherapy (11). Patients were treated with TACE using mitomycin with or without gemcitabine and/or irinotecan. The indication for TACE of liver metastases in patients with colorectal cancer was primarily palliative. The 1-year survival rate after chemoembolization was 62%, and the 2-year survival rate was 28%. The median survival from the start of chemoembolization treatment was 14 months (12). Evidence suggests TACE delivered with embolic beads pre-loaded with a chemotherapeutic agent is comparable in terms of safety and efficacy to conventional TACE (12).

Biocompatible LC beads (Farnham, UK) is a controlled embolization system used for embolizing blood vessels in a variety of hypervascular tumors and arteriovenous malformations. The LC bead is a preformed, microsphere consisting of a biocompatible, sulphonate-modified, N-Fil hydrogel. It is capable of being loaded with several cytotoxic agents with specific ionic properties. The release of the agent takes place over several days to weeks with diffusion of drug into the tissue. The addition of iriotecan to LC beads is considered outside of the Food and Drug Administration approved indication.

The most common complication experienced by almost all patients undergoing chemoembolization is post-embolization syndrome, with pain in the right upper quadrant, nausea, vomiting, fever and elevation of liver enzymes (11).These adverse events are less pronounced when temporary vascular occlusive agents are used (11). Less common complications are liver abscess, tumor rupture, acute liver failure and infarction (1).

Response rates of 13 to 27% were observed in phase II studies of both chemo-naive and 5-FU pre-treated patients using a weekly or three-weekly intravenous infusion schedule. A phase III study comparing irinotecan to best supportive care in patients with 5-FU-refractory disease showed a survival benefit of 2.7 months (13).

Aliberti *et al*. performed a study with 10 patients with liver metastases from CRC who were treated with TACE using DEBIRI at a dose of 100 mg every three weeks. The study showed that this treatment was active and safe (13). In a phase II study, Fiorentini *et al*. performed a clinical trial of TACE with DEBIRI in 20 patients affected by liver metastases from CRC in a palliative setting. They observed a relevant response rate of 16 out of 20, with significant

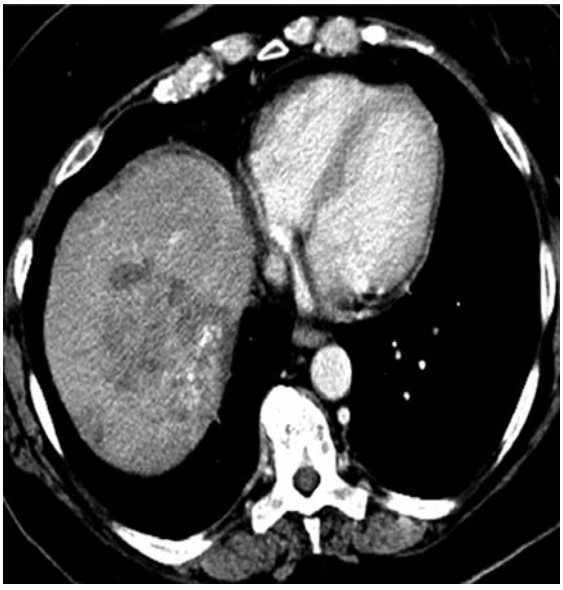

Figure 3. *Triple-phase computed tomographic scan prior to DEBIRI treatment.*

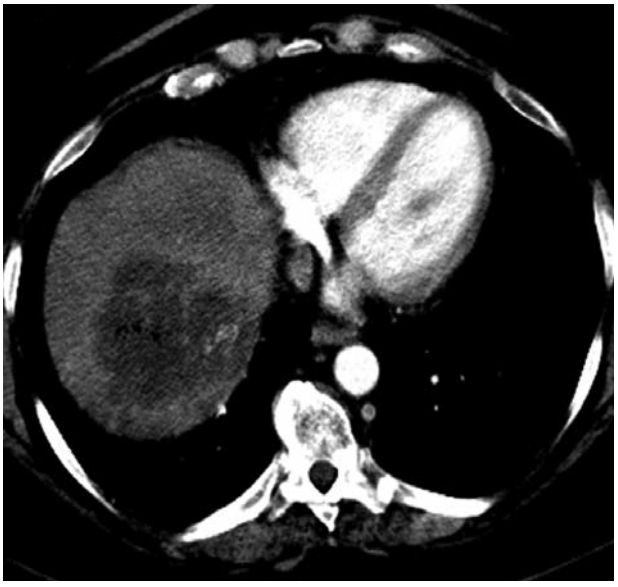

Figure 5. *Triple-phase computed tomographic scan post-DEBIRI treatment.*

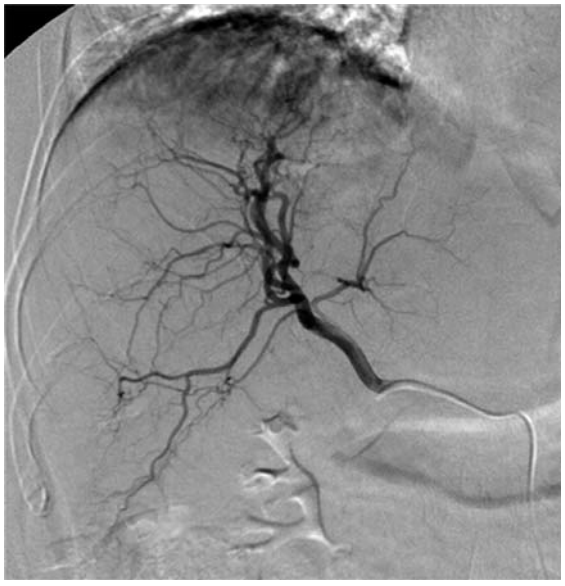

Figure 4. *Treatment by transarterial chemoembolization with DEBIRI.*

reduction of contrast enhancement within lesions in all responding patients. The procedure was well-tolerated by most patients with a median duration of hospitalization of three days. The median follow-up period was 200 days (1). Martin *et al*. published data from a multicenter registry of 30 patients using TACE with DEBIRI who had failed first-line therapy. Fifty-seven embolization sessions were performed, with a median follow-up period of nine months from January 2007 to October 2008. Response rates by modified the RECIST criteria were 75% at three months and 66% at six months. All 30 patients demonstrated a 50% or greater drop in their carcinoembryonic antigen levels at three months that was sustained at the six month evaluation (2). In another study by Martin *et al*., patients with unresectable hepatic metastases from CRC, who had failed standard therapy, were treated with repeat DEBIRI embolizations. Fifty-five patients underwent 99 treatments. The median length of their hospital stay was 23 h and the median disease-free and overall survival from the time of the first treatment was 247 days and 343 days (7), respectively.

The final results of a randomized phase III study on DEBIRI *versus* FOLFIRI for hepatic metastases from CRC demonstrated that progression-free survival for DEBIRI was 7 months compared to FOLFIRI which was only four months. This suggests a benefit of DEBIRI treatment over standard chemotherapy (14).

The results of our retrospective study suggest that TACE with DEBIRI is a safe and effective palliative treatment of hepatic metastases from CRC for patients who have failed at least one line of systemic chemotherapy. In this study population, it was well-tolerated, with a low adverse event profile and acceptable tumor response rates. This is concordant with the results obtained by studies performed by Fiorentini *et al*. and Martin *et al*. (1, 2).

The study is limited by a relatively small sample size and lack of follow-up for all patients; however, as far as we know, this is the first single-institution data collection for

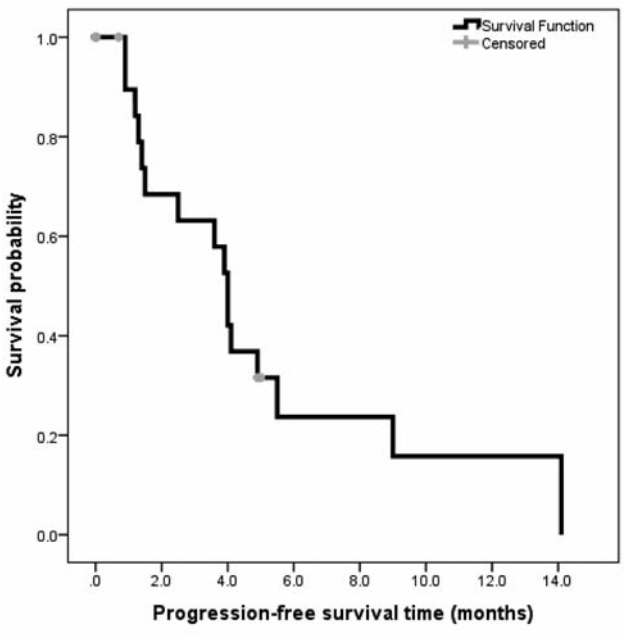

Figure 6. *Progression-free survival of patients treated with transarterial irinotecan drug eluting beads.*

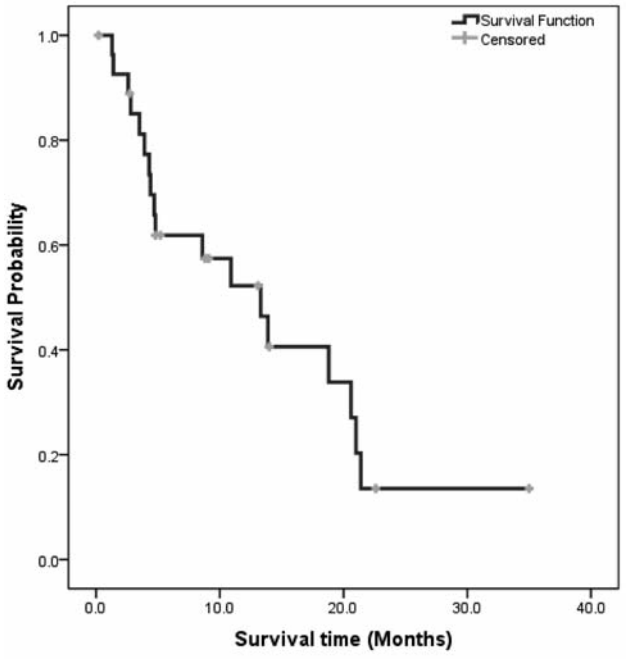

Figure 7. *Overall median survival of patients treated with transarterial irinotecan drug eluting beads.*

US-based patients receiving DEBIRI for metastatic CRC. In this cohort, patients were also treated safely with DEBIRI for bilobar disease in the same session, without significantly increasing the incidence of adverse effects.

Conclusion

The addition of new drugs for the treatment of metastatic CRC has extended the median survival beyond 21 months, but all treatments remain clearly palliative and yet there is no evidence that new therapies, including TACE, improve the cure rate. Palliative therapy with DEBIRI is safe and well-tolerated, thereby offering patients an improvement in their quality of life.

Prolonged follow-up is still being carried out to better define the therapeutic results of this approach.

References

1 Fiorentini G, Aliberti C, Turrisi G, Del Conte A, Rossi S, Benea G and Giovanis P: Intraarterial hepatic chemoembolization of liver metastases from colorectal cancer adopting irinotecan-eluting beads: Results of a phase II clinical study. In Vivo *21(6)*: 1085-1092, 2007.

2 Martin, RCG, Joshi J, Robbins K, Tomalty D, O'Hara R and Tatum C: Transarterial Chemoembolization of Metastatic Colorectal Carcinoma with Drug-Eluting Beads, Irinotecan: Multi-institutional registry. J Oncol *29*: 1-6, 2009.

3 Chong G and Cunningham D: Improving long-term outcomes for patients with liver metastases from colorectal cancer. J Clin Oncol *23(36)*: 9063-9066, 2005.

4 Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM and McWilliams RR: Improved Survival in Metastatic Colorectal Cancer Is Associated With Adoption of Hepatic Resection and Improved Chemotherapy. J Clin Oncol *27(22)*: 3677-3683, 2009.

5 Zorzi D, Mullen J, Abdalla E, Pawlik T, Andres A, Muratore A, Curley S, Mentha G, Capussotti L and Vauthey J: Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. J Gastrointest Surg *10(1)*: 86-94, 2006.

6 Reddy S, Pawlik T, Zorzi D, Gleisner A, Ribero D, Assumpcao L, Barbas A, Abdalla E, Choti M, Vauthey J, Ludwig K, Mantyh C, Morse M and Clary B: Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol *14(12)*: 3481-3491, 2007.

7 Martin RC, Robbins K, Tomalty D, O'Hara R, Bosnjakovic P, Padr R, Rocek M, Slauf F, Scupchenko A and Tatum C: Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: an interim report. World J Surg Oncol. 2009 Nov 3: 7:80. Available at http://www.wjso.com/ content/7/1/80.

8 Kelly H and Goldberg R: Systemic therapy for metastatic colorectal cancer: Current options, current evidence. J Clin Oncol *23(20)*: 4553-4560, 2005.

9 Karapetis C, Khambata-Ford S, Jonker D, O'Callaghan C, Tu D, Tebbutt N, Simes R, Chalchal H, Shapiro J, Robitaille S, Price T, Shepherd L, Au H, Langer C, Moore M and Zalcberg J: K-RAS mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med *359(17)*: 1757-1765, 2008.

10 Lencioni R and Llovet J: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis *30(1)*: 52-60, 2010.
11 Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R and Zangos S: Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: Prospective study. Radiology *250(1)*: 281-289, 2009.
12 Lammer J, Malagari K, Vogl T, Pilleul F, Denys A , Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P and Lencioni R: Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION V study. Cardiovasc Intervent Radiol *33(1)*: 41-52, 2010.
13 Aliberti C, Tilli M, Benea G and Fiorentini G: Trans-arterial Chemoembolization of liver metastases from colorectal cancer using irinotecan-eluting beads: Preliminary results. Anticancer Res *26(5B)*: 3793-3796, 2006.
14 Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, Mambrini A, Montagnani F, Alessandroni P, Catalano V and Coschiera P: Intra-arterial Infusion of Irinotecan-loaded Drug-eluting Beads (DEBIRI) *versus* Intravenous Therapy (FOLFIRI) for Hepatic Metastases from Colorectal Cancer:Final Results of a Phase III Study. Anticancer Res *32(4)*: 1387-1396, 2012.

Received February 21, 2013
Revised March 20, 2013
Accepted March 21, 2013