Review

Chemoembolization in Colorectal Liver Metastases: The Rebirth

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Abstract. *Currently image-guided trans-arterial chemoembolization (TACE) has a significant role in the therapy of patients with hepatocellular carcinoma and liver metastases. This endovascular hepatic-directed therapy offers the dual benefit of true local neoplastic control and reduction of side-effects. As a result, it has been included in the guidelines for primary liver cancer and is often considered as salvage therapy for patients liver metastases from neuroendocrine and chemorefractory colorectal tumors. The development of new embolizing agents, such as DC beads loaded with doxorubicin and irinotecan, permits better standardization and definition of protocols, making the procedures less linked to criteria of different hospitals and personal experiences of interventional radiologists. The understanding that hypoxia induces vessel re-growth will open a new avenue for clinical research and a rebirth for TACE. Chemoembolization followed by target therapy (bevacizumab, aflibercept and regorafenib) could increase quality, duration of responses and better quality of life.*

Large bowel cancer is a leading cause of death, accounting for nearly 10% of all cancer deaths in Western countries (1, 2). Liver metastases (LM) develop in 45% of patients with colorectal carcinoma (CRC) and currently represent a major health challenge (3). Following conventional criteria for resectability, in patients with LMs approximately 70% of cases are considered unresectable (4, 5). Nevertheless, the vast majority of patients undergoing resection will develop recurrent LM within two years of surgery, and approximately 60-90% of patients who were treated with neoadjuvant chemotherapy will experience a recurrence of their liver tumors (5).

For patients who do not undergo surgery, survival rates are disappointing, with 5-year survivals less than 25% (4, 5).

In the past, 5-fluorouracil (FU) and leucovorin (LV) constituted the foundation of most chemotherapy regimens, and response rates have increased from 10% to 30% under their combination (6, 7). Recent years have seen important results in the treatment of advanced CRC, particularly in the use of new chemotherapy approaches and their combination with targeted therapies. A shift toward multi-agent treatment strategies including a variety of chemotherapy drugs and monoclonal antibodies such as bevacizumab, cetuximab and panitumumab has improved response rates and prolonged survival among patients with advanced CRC. Modern regimens such as combined 5-FU/LV with oxaliplatin or CPT-11 and monoclonal antibodies have achieved response rates of approximately 80%, and median survival of patients with non-resectable LM has increased to 20-26 months (8-14).

The potential value of resectability in achieving long-term survival has resulted in the development of oncological strategies for initially non-resectable LM from CRC (15, 16). Even in patients who underwent hepatectomy, tumor relapse in the remnant liver appears frequent and indications for repeat-hepatectomy are limited (17).

The new systemic chemotherapeutic regimens have been associated with skin reactions, high costs and impaired liver functions due to hepatosteatosis and sinusoidal dialation (18). Furthermore, in patients with LM from CRC with limited extra-hepatic metastases, control of liver LM might be related to a better overall survival (19).

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A further goal is therefore how to successfully achieve local control and increase the proportion of patients able to undergo liver resection, reduce recurrences, and prolong survival and quality of life of patients who remain unsuitable for resection.

Several liver-directed therapies have been developed to improve the local control of primary and secondary tumors (20, 21). Conventional TACE and a new type of TACE adopting DC beads (DEB-TACE) are discussed in order to support the integration into the current routine clinical care for the management of liver-only or liver-dominant LM from CRC.

TACE: Rationale, Methods and Materials

The rationale behind intra-hepatic arterial delivery is that, in contrast to normal healthy liver tissue which is supplied by the portal vein, liver tumors (primary and metastatic) receive their blood supply almost exclusively from the artery, which can then be exploited for anatomical targeting and treatment. The concept of TACE is to infuse chemotherapeutic agents followed by embolic particles into the hepatic arteries supplying the liver tumors, while sparing the surrounding normal hepatic parenchyma. TACE is the most commonly performed procedure for liver tumors. Other treatments such as transarterial chemotherapy infusion (TACI), transarterial embolotherapy (TAE) and radioembolization using yttrium-90 are less commonly used.

Recently, a new method has been developed derived from TACE called DEB-TACE, where lipiodol is substituted for polymer-based microparticles (DEB), which results in enhanced drug delivery to the tumor and significant reduction in systemic drug exposure compared to conventional TACE.

TACE has been in clinical practice since the early 1980s and was introduced by Yamada *et al*. (22, 23). The method was suggested to improve TACI by prolonging, by means of embolic particles, the duration of exposure to high concentrations of chemotherapy, with reduced systemic bioavailability. The high first-pass effect of chemotherapy, augmented by prolonged exposure time with high drug levels from embolic effects on the tumor vasculature, produces a significant increase of the pharmacological advantage for regional drug delivery (24).

Doxorubicin is the most commonly used drug for hepatocellular carcinoma, whereas the adoption of cisplatin, FU, doxorubicin and mitomycin are preferred for secondary tumors. The chemotherapeutic agent is usually mixed with an oil-based contrast medium (Lipiodol Ultrafiltrate; Laboratoire Guebert, France). The water-in-oil emulsion obtained is selectively delivered to the tumor-feeding artery, followed by temporary or permanent embolization. Lipiodol is the basic component of conventional TACE and has unique properties as a drug-carrier and embolizing agent. Due to the high vascularization of most liver tumors and the absence of Kupffer cells, lipiodol can persist within tumor nodules for several weeks, thus embolizing tumor vasculature up to capillaries.

Several embolic agents are injected to enhance the effects of intra-arterial drug delivery. Gelfoam, polyvinyl alcohol particles, trisacryl gelatin and degradable starch microspheres are the most commonly used agents (20, 21, 25). The administration of embolic agents has a dual aim: inducing stasis in the segmental arteries and reducing wash-out of the previously deposited emulsion of drug and lipiodol.

The introduction of DEB improved the ability of conventional TACE to administer higher concentrations of chemotherapy to liver carcinomas while reducing the systemic peaks of chemotherapy, thus minimizing side-effects. These microspheres are sized from 75 to 900 μm, and are made of non-degradable material, polyvinyl alcohol (PVA) based hydrogel bead system. They are manufactured by polymerization of methacyloyl-modified PVA macromeres suspended in an oil phase. The macromeres are synthesized by reacting PVA with N-acrylamido-amonoacetaldehyde, followed by co-polymerization with 2-methylpropane sulfonate by free radicals (26). DEB are biocompatible, non-biodegradable, spherical, soft and compressible. Hence, they provide permanent embolization, limiting the number of administrations that can be applied to the tumor through the same blood vessel. The drug uptake occurs through an ion-exchange mechanism. Pharmacological studies have shown that drug elution occurs slowly, with continuous release of doxorubicin from DEB to the tumors (26, 27). The histological reports show high activity of DEB-TACE, causing necrosis and tissue-reactive inflammation. DEB have CE mark approval for TACE of hepatocellular cancer and LM from CRC and can be loaded with doxorubicin and irinotecan, respectively, for drug delivery. Many clinicians in Western countries have adopted DEB-TACE, shifting from conventional TACE, to treat primary and metastatic liver tumors. Rather than DEB, the Food and Drug Administrartion (FDA) has approved as embolic material the DEB made by Biocompatibles-BTG that can be loaded with irinotecan (DEBIRI) or doxorubicin (DEBDOX).

Current Clinical Application: Rescue Therapy For Chemorefractory Metastases from CRC

Conventional TACE is considered the worldwide standard-of-care for patients with unresectable hepatocellular carcinoma who have preserved performance status and liver function without vascular invasion or extrahepatic disease. The procedure has a proven survival benefit when compared to best supportive care in select patient populations with unresectable hepatocellular carcinoma (28). Despite these well-known results obtained for primary liver cancer, there are few data to support its use for the treatment of LM from CRC, where TACE still has limited clinical indication.

In 1998, Tellez *et al*. reported a phase II trial in 30 patients with LM from CRC who had failed standard of care systemic chemotherapy (29). Radiological responses occurred in 63% of patients and 95% had a decrease of at least 25% of the baseline Carcino-Embriogenic Antigen (CEA) level. Median overall survival (OS) for all patients was 8.6 months. The authors concluded that TACE is a feasible treatment that results in high response rates, with mild-to-moderate toxicity for patients with LM from CRC who have experienced failure with other systemic treatments.

Bavisotto *et al*. performed a retrospective study on patients with unresectable LM from CRC, of whom 44% had previously failed one or more systemic chemotherapy options (30). A regimen of alternating regional TACE was delivered between cycles of protracted continuous infusion of FU as systemic chemotherapy. Response rates of up to 70% were observed, with a median OS of 14.3 months. OS at one and two years was 57% and 19%, respectively. The authors concluded that alternating systemic FU and regional TACE is an active and feasible regimen, with manageable toxicities in this patient group.

In 2009, Hong *et al*. reported on patients with CRC of whom the majority had previously been treated with systemic chemotherapy, and demonstrated that TACE and radioembolization can prolong survival (31). Albert *et al*. reported that TACE with cisplatin, doxorubicin, mitomycin C, ethiodized oil, and PVA particles was performed at monthly intervals for one to four sessions to pre-treated patients with LM from CRC. A second cycle was performed for intra-hepatic recurrence. A total of 245 treatments were performed over 141 cycles on 121 patients. Ninety-five out of 141 treatment cycles were evaluable for response: two (2%) partial responses, 39 (41%) cases of stable disease, and 54 (57%) of progression resulted. Median time-to-disease progression (TTP) in the treated liver was five months, and median TTP anywhere was three months. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and nine months from chemoembolization. Survival was significantly better when chemoembolization was performed after first- or second-line systemic therapy (11-12 months) than after third- to fifth-line therapies (six months) (p=0.03). Presence of extrahepatic metastases did not adversely affect survival (p=0.48). Albert *et al*. concluded that TACE provided local disease control of LM after 43% of treatment cycles. Median survival was 27 months overall, and 11 months when initiated for salvage after failure of second-line systemic therapy (32).

Nishiofuqu *et al*., in a phase I/II study in 24 patients with unresectable LM from CRC, reported on the use of TACE after failure (33). In the phase II portion, a tumor response rate of 61.1% was achieved, with a median hepatic progression-free survival (PFS) and OS of 8.8 months and 21.1 months, respectively. The procedure was generally well-tolerated (33).

Vogl *et al*. treated 463 patients with pre-treated unresectable LM of CRC with TACE in 4-week intervals (34). The local chemotherapy protocol consisted of mitomycin C alone (n=243), mitomycin C with gemcitabine (n=153), or mitomycin C with irinotecan (n=67). Embolization was performed with lipiodol and starch microspheres for vessel occlusion. Evaluation of local tumor control resulted in partial response (14.7%), stable disease (48.2%), and progressive disease (37.1%). The 1-year survival rate after chemoembolization was 62%, and the 2-year survival rate was 28%. Median survival from the start of TACE was 14 months. There was no statistically significant difference between the three treatment protocols. They concluded that TACE is a minimally-invasive therapy option for palliative treatment of liver metastases in patients with colorectal cancer, with similar results among three chemoembolization protocols.

Sanz Altamira *et al*. treated 40 patients with TACE of the feeding vessels of the metastatic lesions from CRC (35). They injected chemoemulsion consisting of 1,000 mg of 5-fluorouracil, 10 mg of mitomycin C, and 10 ml of ethiodized oil in a total volume of 30 ml. Gelfoam embolization then followed, until stagnation of blood flow was achieved. Overall median survival from date of first chemoembolization was ten months. Factors that predicted a longer median survival included favorable performance status (24 months), serum alkaline phosphatase and lactate dehydrogenase levels less than three-times normal (24 and 12 months, respectively), and metastatic disease confined to the liver (14 months). The most common side-effects were transient fever, abdominal pain, and fatigue. This study suggests that TACE should be further evaluated; it may be beneficial in patients who have failed systemic chemotherapy.

Salman *et al*. carried-out a prospective randomized phase II trial of hepatic artery embolization *versus* TACE to evaluate the response rates and toxicities in the second-line setting (36). Patients were randomized to receive either embolization therapy with polyvinyl alcohol foam (Ivalon) administered as a single agent or chemoembolization using polyvinyl alcohol foam mixed with 750 mg/m^2 of 5-fluorouracil and 9 million units of interferon. There were 24 patients in the TACE arm and 26 in the embolization arm. Four patients (15.4%) treated with embolization had a partial response, and 5 patients (20.8%) treated with TACE had a partial remission (PR). The median survival for all patients was 11 months.

Hunt *et al*. published the only randomized controlled trial comparing no treatment with TAE and TACE (34). Sixty-one patients were randomized, 20 to receive no treatment, 22 to receive TAE, and 19 to receive intra-arterial infusion of 5-FU followed by embolization with degradable starch microspheres (TACE). Both treatments were acceptable from the patients in terms of low treatment morbidity rate. Median

survival from diagnosis of metastases was 9.6 months for controls, 8.7 months for the TAE group and 13.0 months in the TACE group. There was no apparent survival benefit for the TAE group. The increased survival in the TACE group was observed in all the subgroups analyzed but failed to reach statistical significance. The greatest observed benefit was achieved in the subgroup with less than 50% hepatic replacement with tumor at-presentation (median survival from diagnosis 10.0 months for controls, 10.2 months for TAE and 23.6 months for TACE); 36% of patients developed extra-hepatic disease recurrence. No significant benefit was shown from either TAE or TACE, but a more carefully selected group of patients with only low-volume hepatic disease may benefit from TACE therapy.

Even if all these studies reported interesting results, the treatment guidelines of the National Comprehensive Cancer Network (NCCN) version 1.2013 actually consider TACE a category 3 recommendation based on insufficient data and variations in techniques among institutions (38).

Table I outlines key studies using conventional TACE in the treatment of not resectable LM from CRC.

DEB-TACE

In 2006, DEB-TACE was introduced into clinical trials. The unique properties of DEB, once injected into the tumor-feeding arteries, is a slow and controlled release of the drug, which results in a significant cancer cell killing. Significant reductions in peak plasma concentrations have been reported when compared with conventional TACE (27), which may enable patients to better-tolerate the cytotoxic agents used (39). Due to sustained release, greater amounts of the chemotherapeutic agent are maintained in the tumor, resulting in a more evidenced necrosis.

Like conventional TACE, DEB-TACE is mainly considered as a palliative option for patients with unresectable hepatocellular carcinoma who have preserved liver function and performance status and is called DEBDOX because doxorubicin has been charged on DEB. DEB-TACE may also be used for the palliation of not resectable LM from CRC (40-45), and is known as DEBIRI because irinotecan has been charged on DEB.

Martin *et al*. conducted a phase I trial with irinotecan DEBs combined with concomitant systemic fluorouracil and oxaliplatin (FOLFOX) in 10 chemonaïve patients with unresectable LM from CRC. The initial 9 and 12 month response rates were 100% (2 CR, 8 PR), and 40% of patients were successfully down-staged to resection with/without ablation, with a median OS of 15.2 months. Adverse events were minimal, with no dose-limiting toxicities (40).

Aliberti *et al*. recently reported on a phase II study of DEBIRI in 82 patients with LM from CRC who had failed previous chemotherapy. Responses were 78% at three months, with a median duration of response of six months. The median OS was 25 months with PFS of eight months. The authors concluded that DEBIRI could be proposed as palliative therapy for unresectable and chemotherapy-resistant LM from CRC (41).

Martin *et al*. reported findings of a single-arm study of patients with advanced LM from CRC receiving DEBIRI. All patients had failed oxaliplatin- and irinotecan-based systemic chemotherapy and biological agents. The study met its primary endpoints by demonstrating that DEBIRI is safe and well tolerated. Response rate was 66% at six months and 75% at 12 months. OS was 19 months, with PFS of 11 months. The authors concluded that the ability to deliver a large dose of hepatic-specific cytotoxic agents to the liver can potentially lead to improvements in response rates and PFS (42).

Eihcler *et al*. carried-out a pilot clinical study to assess the safety, technical feasibility, pharmacokinetic (PK) profile and tumor response of DEBIRI. Eleven patients with a tumor burden <30% of the liver volume, received up to 4 sessions of DEBIRI at 3-week intervals. PK was measured after the first cycle. Patients were followed-up for 24 weeks. Only mild-to-moderate adverse events were observed. Average C_{max} for irinotecan and SN-38 was 194 ng/ml and 16.7 ng/ml, respectively, with an average $t_{½}$ of 4.6 h and 12.4 h following administration of DEBIRI. Best overall response during the study showed disease control in 9 patients: 2 patients with partial response and 7 with stable disease, overall response rate of 18% (43).

Fiorentini *et al*. carried-out a first phase II study on 20 patients reporting significative response rates of 65% and overall survival of 14 months (44). Then they conducted the only randomized controlled trial comparing DEBIRI with systemic chemotherapy (FOLFIRI) for LM from CRC (45). Seventy-four patients were randomly assigned to receive DEBIRI (36 patients), *versus* 38 patients receiving systemic irinotecan, fluorouracil and leucovorin (FOLFIRI). The primary end-point was survival; secondary end-points were response, recurrence, toxicity, quality of life, cost and influence of molecular markers. At 50 months, OS was significantly longer for patients treated with DEBIRI than for those treated with FOLFIRI (log-rank p=0.031). Median survival was 22 (95% confidence interval (CI)=21-23) months, for DEBIRI and 15 (95% CI=12-18) months for FOLFIRI. PFS was 7 (95% CI=3-11) months in the DEBIRI group compared to 4 (95% CI=3-5) months in the FOLFIRI group, and the difference between groups was statistically significant (log-rank p=0.006). Extra-hepatic progression had occurred in all patients by the end of the study, at a median time of 13 (95% CI=10-16) months in the DEBIRI-group compared to 9 (95% CI 5-13) months in the FOLFIRI-group. A statistically significant difference between groups was not observed (log-rank p=0.064). The median time for duration of improvement to quality of life was 8 (95% CI=3-13) months in the DEBIRI-group and 3 (95% CI=2-4)

Table I. *Key studies adopting conventional TACE in the treatment of not resectable LM from CRC.*

Author	Patients	Line of therapy	Drugs adopted	Embolic agent used	ORR %	PFS (months)	OS (months)
HUNT (37)	19	FL	FU	DSM	n.r	n.r	13
SANZ ALTAMIRA (35)	40	FL	FU, MITO	Ethiodized oil, Gelfoam	n.r	n.r	10
TELLEZ (29)	30	SL	CDDP, DOXO, MITO	Gelfoam	63	n.r	8.6
BAVISOTTO (30)	20	SL	CDDP	PVA	70	4.2	14.3
SALMAN (36)	24	SL	FU	PVA	20.8	n.r	11
HONG (31)	21	SL	CDDP, DOXO, MITO	PVA	n.r	n.r	7.7
VOGL (34)	463	STL	MITO, GEM, IRI	Ethiodized oil, DSM	14.7	n.r	14
ALBERT 2011 (32)	121	SL	CDDP, DOXO, MITO	Ethiodized oil, PVA	43	5	11
NISHIOFUKU 2012 (33)	24	SL	CDDP	DSM	61.1	8.8	8.8

FL: first line; SL: second line; STL: second and third line; FU: fluorouracil; MITO: mitomycin; CDDP: cisplatin; GEM: gemcitabine; IRI: irinotecan; DOXO: doxorubicin; DSM: degradable starch microspheres; PVA: polyvinyl alcohol microspheres; n.r.: not reported; ORR: overall response rate; OS: overall survival.

Table II. *Key studies adopting DEBIRI in the treatment of not resectable LM from CRC.*

Author	Patients	Line of therapy	Drugs adopted	Embolic agent used	ORR %	PFS (months)	OS (months)
MARTIN (40)	55	STL	IRI	DC Bead	66 at 6 months 75 at 12 months	11	19
ALIBERTI (41)	82	STL	IRI	DC Bead	78	8	25
MARTIN (42)	10	FL	IRI (+ FOLFOX)	DC Bead	100	n.r	15.2
EICLHER (43)	11	TL	IRI	DC Bead	18	n.r	n.r.
FIORENTINI (44)	20	TL	IRI	DC Bead	65	6	14
FIORENTINI (45)	36	STL	IRI	DC Bead	68.6	7	22
	38		FOLFIRI		20	4	15

FL: first line; SL: second line; TL: third line; STL: second and third line; IRI: irinotecan; FOLOFOX: folinic acid, fluorouracil and oxaliplatin given intravenously; FOLFIRI: folinic acid, fluorouracil and irinotecan given intravenously; n.r.: not reported; ORR: overall response rate; PFS: period free survival; OS: overall survival.

months in the FOLFIRI-group. The difference in duration of improvement was statistically significant (log-rank p=0.00002). This study showed a statistically significant difference between DEBIRI and FOLFIRI for OS (7 months), PFS (3 months) and quality of life (5 months). In addition, a clinically significant improvement in time-to-extra-hepatic progression (4 months) was observed for DEBIRI, a reversal of the expectation for a regional treatment. The response rate was 68.6% and 20%, for DEBIRI and FOLFIRI, respectively. This suggests a benefit of DEBIRI treatment over standard chemotherapy and serves to establish the expected difference between these two treatment options for planning future large randomized studies (45).

The treatment guidelines of the NCCN v. 3.2013 advises that DEBIRI should be considered selectively and only at Institutions with experience. No category recommendations are reported (38).

Table II outlines key studies using DEBIRI in the treatment of not resectable LM from CRC.

Improvements in Chemoembolization Results

The main effects of conventional TACE and DEB-TACE are ischemia and delivery of high drug concentrations to cancer cells. Although these methods can cause massive tumor necrosis, tumor recurrences are observed. It has been hypothesized that the cause is the stimulation of neoangiogenic pathways that are up-regulated within a few hours after TACE, presumably as a result of the hypoxia caused by the infarction of the tumor. Many markers of hypoxia, such as hypoxia-inducible factor-1α, vascular endothelial growth factor (VEGF) are up-regulated and could start stimulation of neoangiogenesis. VEGF/VEGFR signaling is a pro-angiogenic pathway and the ligands include VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor (PIGF) that interact with membrane-bound tyrosine kinase receptors VEGFR-1 (FLT-1), VEGFR-2 (FLK-1/KDR) and VEGFR-3 (FLT4) (46, 47). The binding

of VEGF-A (or VEGF) to VEGFR-2 had been found to be a key mediator of angiogenesis. VEGF-A (commonly known simply as VEGF) is expressed in many human carcinomas and binding with VEGFR-2 in the tumor microenvironment triggers a number of intracellular signaling cascades in endothelial cells, leading to the formation and enhancement of tumor microvasculature. Today, well-known agents, such as bevacizumab, and new ones, such as aflibercept and regorafenib, offer interesting possibilities to reduce relapse and prolong PFS and survival after TACE.

Bevacizumab. A recombinant humanized monoclonal IgG1 antibody, bevacizumab binds to and inhibits the biologic activity of VEGF by preventing its binding to VEGFR-1 and VEGFR-2. The therapeutic role of bevacizumab in treating metastatic CRC is well-established and supported by well-conducted randomized trials (11-15, 48, 49). Recently, the benefit of continuing angiogenic suppression beyond first disease progression in LMs from CRC was confirmed in patients in a randomized phase III trial: bevacizumab beyond disease progression, while switching the cytotoxic chemotherapy, improved the PFS (5.7 *vs*. 4.1 months) and OS (11.2 *vs*. 9.8 months) in the group that continued bevacizumab compared to those who did not (49).

Aflibercept. Also known as VEGF Trap, aflibercept is a recombinant fusion protein consisting of the extracellular domains of human VEGFR-1 and -2 fused to the Fc portion of human IgG1 (50). The decoy protein binds to VEGF-A, VEGF-B and PIGF and prevents the activation of VEGFR-1 and VEGFR-2 by these ligands, in contrast to bevacizumab which binds VEGF-A only (51, 52). Compared to bevacizumab, aflibercept has a higher affinity for VEGF-A and its native receptor. Aflibercept was evaluated in combination with various chemotherapeutic agents including FOLFOX 4, irinotecan with FU and leucoverin (53-56) in patients with advanced CRC and other solid tumors. Aflibercept was also evaluated in combination with irinotecan, 5-FU and LV in a dose-escalation study. As such, 4 mg/kg aflibercept dose level was selected for further development in combination with irinotecan, 5-FU and LV. The pharmacokinetic studies showed that the elimination half-life of aflibercept ranged from less than 1-3 days for free aflibercept, and was approximately 18 days for VEGF-bound aflibercept (56, 57, 58).

The benefit of aflibercept in combination with FOLFIRI was confirmed in the pivotal phase III VELOUR trial (59). In that study, patients with metastatic CRC previously treated with oxaliplatin-containing regimen, regardless of prior bevacizumab treatment, were randomly assigned to received aflibercept at 4 mg/kg *i.v.* every two weeks or placebo combination with FOLFIRI. The overall response rate was 19.8% in the aflibercept arm compared to 11.1% in the placebo arm (p=0.0001). Compared to the control group, the aflibercept-containing arm had better PFS (6.9 *vs*. 4.67 months; hazard ratio (HR)=0.758; p<0.0001) and OS (13.5 *vs*. 12.06 months; HR=0.817; p=0.0032). Pre-planned subgroup analysis showed that prior bevacizumab use did not influence the effect of aflibercept on PFS and OS, although the study was not powered to show a treatment difference between arms (59). Toxicities related to aflibercept were consistent with those expected from the anti-VEGF drug class. Together with the results from the ML18147 study (58), clinicians now have the option of using bevacizumab or aflibercept with FOLFIRI in patients with advanced CRC who progressed following oxaliplatin-containing regimen. The benefit achieved by aflibercept and bevacizumab in the second-line setting seemed comparable: in the ML18147 study, continuing bevacizumab into second line while switching the cytotoxic chemotherapy achieved a median OS improvement of 1.4 months (HR=0.81, 95% CI=0.69-0.94; p=0.0062), whilst the addition of aflibercept to FOLFIRI in the VELOUR trial achieved a comparable median OS survival improvement of 1.4 months (HR=0.817, 95.34% CI=0.713-0.937; p=0.0032). The frequency of vascular-related adverse events seemed to be higher with aflibercept than bevacizumab treatment when comparing across trials. Cost is another consideration: aflibercept treatment costs on average in the US are in the area of $11,000 per month, which is more than twice as high as bevacizumab therapy.

Regorafenib. Related to sorafenib, regorafenib is slightly structurally different, resulting in higher inhibitory potency against various pro-angiogenic receptors, including VEGFR2 and FGFR1 (60, 61). Other receptor kinases inhibited by regorafenib include VEGFR1, -3, RAF, TIE2, and mutant oncogenic kinases KIT, RET and BRAF (62). Regorafenib showed significant anticancer efficacy in CRC and other tumor types (63, 64). In an expanded phase I study specific for relapsed or refractory advanced CRC, 38 patients received regorafenib dose levels ranging from 60-220 mg daily administered on a 21 days on followed by seven days off dosing schedule. Enrolled patients had received a median of four previous lines of treatment. In efficacy evaluation, 27 evaluable patients achieved 74% disease control rate with partial response in one patient (4%) and stable disease in 19 (70%). Overall, regorafenib was well tolerated and adverse events were manageable (65).The multinational phase III CORRECT trial enrolled patients with advanced CRC who had received all locally approved standard therapies and in whom disease had progressed during or within three months after the last standard therapy (66). Patients were randomized at a 2:1 ratio to receive regorafenib or placebo. Five hundred patients received regorafenib at 160 mg orally 21 days on seven days off and 253 patients received placebo. Median OS was 6.4 months in the regorafenib group *versus* 5.0 months in the placebo group (HR=0.77; 95% CI=0.64-0.94; one-

sided p=0.0052). The most common treatment-related grade 3 or worse adverse events were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash or skin desquamation (6%), consistent with that observed in earlier phase trials. These adverse events were mostly manageable with dose reduction or interruption.

Discussion

TACE has a long history and has led to better patient survival while permitting a good quality of life, and as a result has been introduced into the guidelines for primary liver cancer and is considered, and used worldwide, in the treatment of metastatic disease from neuroendocrine tumors and CRC. Some unclear points persist: lack of standardized protocols and of a definitive and clear position in the program of patients care. This aspect makes the procedures dependent on personal criteria and individual capacity.

TACE and DEBIRI have been proven safe and effective in salvage treatment of non-responsive LM from CRC, and are more frequently used than in the past.

Several retrospective studies suggest that conventional TACE is associated with improved survival in patients with chemorefractory LM from CRC without heavy or unacceptable toxicity (29-37). Phase II/III data of DEB-TACE in chemorefractory patients achieved response rates around 70%, with median survival times of 22-25 months and PFS of 7-8 months (40-45). These results are encouraging and indicate that DEBIRI could be proposed as palliative therapy for unresectable and chemorefractory LM from CRC.

The phase III trial also provided evidence that infusion of DEBIRI offers superior survival with better quality of life when compared with the same chemotherapy administered intravenously (45) .

Richardson *et al*. carried-out the first comprehensive search of medical literature identified studies describing the use of DEBIRI in the treatment of LMs from CRC (67). Data describing side-effects, tumor response, pharmacokinetics and OS were collected. Five observational studies and one randomized controlled trial were reviewed. A total of 235 patients were included in the descriptive analysis of observational studies. Post-embolization syndrome was the most common adverse event. Peak plasma levels of irinotecan were observed at 1-2 h after administration. Wide variations in tumor response were observed. The median survival time ranged from 15.2 months to 25 months. They underlined that in the randomized controlled trial of Fiorentini *et al*., treatment with DEBIRI was superior to systemic chemotherapy with FOLFIRI in terms of quality of life and PFS. For patients with unresectable LM, particularly after failure to respond to first-line regimens, DEBIRI represents a novel alternative to systemic chemotherapy alone, conventional TACE with other agents, or other local treatments (radiofrequency ablation). They conclude that further randomized controlled trials comparing DEBIRI with alternative management strategies are required to define the optimal role for this treatment.

Based on previous clinical data and on the well-known phenomenon of neoangiogenesis, it is more logical and more evident that TACE will be the first step (as macro-antiangiogenic therapy) followed by new target drugs (such as molecular antiangiogenic therapy) to reduce relapses and prolong PFS and survival, optimizing the continuum of care. The development of microspheres capable of loading drugs and their combination with new biological agents directed against vessel re-growth will open new avenues for research and confirm that today there is a true rebirth of chemoembolization.

Based on these data, the use of bevacizumab, aflibercept, and regorafenib could be a significant further step in combination with DEBIRI to increase clinical positive results.

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