Transarterial Therapy for Colorectal Liver Metastases

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KEYWORDS

- Hepatic arterial therapy (HAT) • Chemoembolization • Hepatic artery infusion (HAI)
- Colorectal liver metastases • Surgical resection • Yttrium-90
- Drug-eluting beads (DEB)

KEY POINTS

- Hepatic arterial therapy (HAT) represents a minimally invasive fluoroscopy-guided transarterial catheter-directed therapy that has been used for the treatment of colorectal liver metastases; its primary goal is high-dose local regional drug delivery. Therapy-associated complication rates are low.
- New HAT-drug-eluting bead (DEB) technologies lead to significantly increased cytotoxic drug concentrations in the target liver metastases with lower systemic toxicity than systemic treatments.
- Repeat HAT-DEB procedures augment tumor response to treatment. Repeat Yttrium-90 treatments should be performed with the understanding that repeat treatments increase the possibility of producing durable refractory radiation-induced liver dysfunction.
- HAT may augment the results of first-line systemic chemotherapy in the treatment of patients with unresectable colorectal liver metastases. It may represent a valuable tool in the preoperative management of potential surgical candidates as a method for downsizing and for early conversion to resectability without adverse effects associated with systemic chemotherapy.
- HAT could potentially be used after surgery or ablative therapy to prevent local recurrence with the aim of improving overall survival without major side effects.

BACKGROUND

Colorectal liver metastases (CLM) represent the fourth most common malignancy, and the second most common cause of cancer-related death in Western countries. The presence and extent of liver metastases are major prognostic factors with respect

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to overall survival (OS). At the time of diagnosis of colorectal cancer, 25% to 50% of patients exhibit liver metastases. Furthermore, up to 80% of patients diagnosed with colorectal cancer will develop liver metastases on follow-up evaluation. Because the microstructure of the liver is an effective tumor cell barrier, early distant metastasis due to hematogenous spread is rare. A variety of therapies exist for the treatment of CLM—surgical resection, systemic chemotherapy (CTx), molecular substances, and local ablative treatments. What constitutes the optimal treatment strategy for a given patient depends on tumor stage, mutation status, sequence and pattern of metastases, performance status, and patient preference.[1,2]

Surgical resection is currently accepted as optimal first-line treatment. Resectability with curative intent can be characterized by 5 isolated metastases per liver lobe or less, at least 2 tumor-free adjacent liver segments, and a volume of the liver remnant greater than 20% by reference to the initial liver volume.[3,4] At the time of diagnosis, less than 20% of patients have resectable CLM,[3,4] and 60% to 80% of those undergoing resection will develop recurrent colorectal metastases at follow-up, of which half have a recurrence within the liver.[5,6]

The greater than 80% of patients who do not qualify for CLM resection at the time of diagnosis receive CTx and/or biologic therapy according to the current available European guidelines.[1] Currently, 5-fluorouracil (5-FU) -based regimens consisting of 5-FU, irinotecan, and/or oxaliplatin (eg, FOLFOX, FOLFIRI, and FOLFOXIRI) result in response rates and median OS of 40% to 57% and 15 to 20 months, respectively, but reported 5-year OS rates are still close to 0%.[1,2,7–12] On average, the median OS of patients with stage IV colorectal cancer approximates 21 months with multiagent chemotherapy (intravenous 5-FU plus irinotecan/oxaliplatin). The introduction of molecular substances such as antiepidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) antibodies have further improved outcomes after administration of systemic therapies. Controlled trials showed that the addition of a monoclonal antibody to CTx regimens increased OS to more than 24 months.[1,13]

Current evidence suggests that CTx with or without the use of biologic agents followed by liver resection is safe and effective for selected patients with initially unresectable CLM.[14–18] Use of hepatic arterial therapy (HAT) toward the same end represents an enticing concept, because it allows for markedly higher concentration of drugs or radiation therapy within target liver area, while decreasing the systemic toxicity and adverse effects of CTx or external beam radiation therapy.[19]

TRANSARTERIAL HEPATIC THERAPY

Rationale

Although normal liver parenchyma is largely supplied by the portal vein, malignant liver tumors derive their blood supply from hepatic arterial branches.[20] Thus, transarterial drug delivery into the liver allows a considerably increased local drug concentration/radiation dosage compared with CTx/external beam radiation therapy. At the same time, healthy nonaffected liver parenchyma can be spared, and the liver toxicity that is observed after systemic applications is avoided or at least minimized. Chemotherapy-associated liver injury (CALI; eg, sinusoidal obstruction syndrome [SOS] and nonalcoholic steatohepatitis [NASH])—are relevant limitations to cytotoxic therapy that impact preoperative treatment plans. Hepatic steatosis without inflammation (simple steatosis) may occur with chemotherapy. SOS may occur with oxaliplatin treatment, with increased severity associated with prolonged treatments (>6 cycles). Bevacizumab can be used safely in the preoperative setting when discontinued at

least 5 weeks before liver resection and seems to decrease the incidence and severity of sinusoidal injury after oxaliplatin therapy.[21]

For patients with unresectable liver-only metastases, a response to chemotherapy/radiotherapy could enable resection and should be considered an initial treatment goal. For such patients, oxaliplatin- or irinotecan-based combinatorial regimens represent first-line systemic treatment. The addition of bevacizumab may increase response rates and possibly reduce the risk of CALI.[2] In KRAS wild-type tumors, anti-EGFR antibodies may also augment response rates and improve survival.[2,22]

Unlike systemic administration of chemotherapy, transarterial administration does not force drugs to undergo first-pass metabolism by hepatocytes before reaching their targets. As a result, lower volumes of drugs can result in higher drug concentration within target liver lesions while resulting in less systemic toxicity.[19]

Because angiogenesis is integral to hematogenous spread of primary tumors as well as growth of distant metastases, epidermal growth factor, VEGF, angiopoietin, and cyclo-oxygenase all represent potential targets to modulate the arterial blood supply of CLM. The exact role of these pathways and targeted biologic therapies with respect to treatment of colorectal cancer remains nebulous. Although cetuximab and bevacizumab have been used in the treatment of ependymoma and glioblastoma, respectively, no groups have reported transarterial use of biologic agents in treatment of CLM.[23,24]

Reported Techniques

Because of the lack of an evidence-based treatment standard, multiple chemotherapeutics and embolic agents are used in different combinations and doses.[25–27] Historically, transarterial therapies have been classified as (1) conventional transarterial chemoembolization (cTACE), (2) degradable starch microsphere chemoembolization (DSM-TACE), and (3) hepatic arterial drug-eluting bead therapy (HAT-DEB). Currently, the latter two modalities comprise the majority of the transarterial treatments for CLM.

cTACE involves direct injection of chemotherapeutics into the hepatic arterial system followed by infusion of a vascular occlusive agent such as gelfoam to induce embolization. For DSM-TACE, one or more chemotherapeutics (eg, mitomycin C, gemcitabine, and/or irinotecan) are mixed with DSMs (allowing both to be infused simultaneously), or DSMs are used after treatment to induce embolization.[28,29] In both methods, solutions are injected directly into the right and left hepatic arteries after gaining access to the arterial circulation via the femoral artery. The solution is injected into target areas over a period of approximately 10 minutes. Preinfusion embolization of gastric or duodenal arterial branches is performed in situations whereby there is concern for infusion overflow into these vessels. In cTACE, infusion of a solution containing a vascular occlusive agent is then performed; that agent is a DSM in DSM-TACE. cTACE results in permanent arterial embolization, whereas DSM-TACE induces only temporary vascular occusion because human serum amylase dissolves the DSMs. In Europe, available DSMs (EmboCept S; PharmaCept, Berlin, Germany) have a mean microsphere diameter of 50 μm and a recanalization time of about 60 minutes. **Table 1** lists various published studies examining the safety and efficacy of various different cTACE and DSM-TACE regimens.

Recently, HAT-DEB has become an increasingly popular embolization technique. The concept is based on loading permanent microspheres with a cytotoxic drug such as irinotecan and doxorubicin. After intra-arterial injection of DEBs, a controlled drug release occurs over a period of hours to days within the target tissue.[38] Because the type and dose of the chemotherapeutic can be selected individually and combined

Table 1
Original studies of safety and efficacy of conventional transarterial chemoembolization and degradable starch microsphere for colorectal liver metastases

Reference	Patients (n)	Therapy Stage (1st Line, 2nd Line, 3rd Line, Beyond 3rd Line)	Chemoembolics (Embolic Agents + Chemotherapeutics)	Median Follow-Up (mo)	Progression-free Survival (mo)	Median OS (mo)
Ceelen et al,[30] 1996	14 9	NR	Lipiodol and gelfoam + cisplatin + surgery Surgery alone	15.5 17.5	NR	NR
Tellez et al,[31] 1998	30	NR	Bovine collagen material + cisplatin, doxorubicin, and mitomycin C	NR	NR	8.6
Leichman et al,[32] 1999	31	NR	Collagen suspension + doxorubicin, mitomycin C, and cisplatin	NR	8	14
Müller et al,[33] 2001	103 —	Beyond 2nd line	Group A: HAI 5-FU × 4 d; HAI granulocyte-macrophage colony-stimulating factor (GM-CSF) × 2 d; cTACE lipiodol, gelfoam, melphalan × 1 d Group B: HAI 5-FU/leucovorin/GM-CSF × 2 d; cTACE lipiodol, gelfoam, melphalan × 1 d	42 —	7 8	17 28
Salman et al,[34] 2002	26 24	2nd line	Polyvinyl alcohol (PVA) PVA AND 5-FU + IFN	NR	4 3	10 15
Tsuchiya et al,[29] 2007	27	NR	DSMs + irinotecan and mitomycin C	NR	NR	NR
Vogl et al,[35] 2009	463	2nd line	Lipiodol and DSMs + mitomycin C alone (52.5%), mitomycin C, and gemcitabine (33.0%) or mitomycin C and irinotecan (14.5%)	NR	NR	14
Albert et al,[36] 2011	121	Beyond 2nd line	Lipiodol and PVA + mitomycin C, doxorubicin, cisplatin	NR	3	9
Nishiofuku et al,[28] 2013	24	Beyond 2nd line	DSMs + cisplatin powder	17.4	8.8	21.1
Gruber-Roth et al,[37] 2014	564	NR	Lipiodol AND mitomycin C OR mitomycin C + irinotecan OR mitomycin C + irinotecan + cisplatin	NR	NR	14.3

Data from Refs.[28–37]

with a particular microsphere size and volume, HAT-DEB is gaining significant popularity among HATs in the treatment of CLM.

Tables 2 and 3 provide an overview of (1) chemotherapeutics and biologic agents available for transarterial use and (2) embolic agents used for HAT. With respect to tumor response, it remains unclear which specific combination of drug and embolic agent should be used for an optimal treatment result. The predefined calibration of microsphere size allows an exact control of the embolization depth, whereby the occluded vessel diameters correspond to the nominal diameter of the microsphere. Only randomized controlled studies can determine which chemoembolics result in the best tumor response rates. In contrast to permanent embolic agents, DSMs result in reduced ischemic effects and, therefore, less neoangiogenesis. Future studies examining the use of angiogenesis inhibitors such as bevacizumab in conjunction with HAT are warranted to further address the issue of neoangiogenesis in the setting of HAT.

HEPATIC ARTERIAL DRUG-ELUTING BEAD THERAPY

Rationale

HAT-DEB is a minimally invasive image-guided transarterial liver-directed therapy. After lobar, selective, or superselective injection of one or more chemotherapeutic drugs and one or more embolic agents into the arterial blood supply to liver metastases, combined antitumoral effects (chemotoxicity and ischemia) are observed. The use of an embolic agent before and/or after transarterial drug application results in a reduction of the arterial flow, combining reduced chemotherapeutic clearance with decreased tumor perfusion; however, this can lead to great toxicity and worse adverse effects.[19,58] Some investigators think that achieving stasis for metastatic colorectal disease can lead to enhanced outcomes; however, the degree of stasis has never proven to be a predictor of outcomes.[4,30,58–61] According to the current guidelines, and in contrast to hepatocellular carcinoma, HAT-DEB is still *not* recommended as a standard therapy for CLM. Nevertheless, use of this technology for treatment of CLM is increasing, and recent studies have shown efficacy of repetitive HAT-DEB in patients with liver-dominant colorectal metastases after failure of surgical, ablative, and/or systemic therapies.

Technique

HAT-DEB is indicated for patients with a life expectancy greater than 3 months and an appropriate health status (Eastern Cooperative Oncology Group status $\leq$2).[20,25] Patients must have adequate liver function: bilirubin less than 3 mg/dL, albumin greater than 3 g/dL, and international normalized ratio >1.6. Preinterventional staging (ie, <1 month from treatment) with high-quality thin-cut triphasic contrast-enhanced computed tomography (CT) or dynamic MRI before conventional catheter angiographies are necessary to adequately assess the biology of the disease and to ensure liver-only or liver-dominant disease. Peri-interventional medications include analgesics and antiemetics. In cases of large tumor volumes, intravenous corticosteroids (eg, dexamethasone 250 mg) can effectively treat the tumor edema after HAT-DEB. Prophylactic antibiotics to prevent bloodstream and/or intrahepatic infections are recommended only in high-risk patients.[62]

The correct choice of the catheter position for drug delivery as well as the DEB endpoint are key factors for safe and effective treatments, and both must consider the amount of drug to be delivered (ie, number of vials of beads), size, location, and vascularization of the liver metastases. Treatment via the right or left hepatic artery

Table 2
Chemotherapeutics (including molecular substances) available for transarterial use

Type	Maximum Single Dose	Major Indications	Major Toxicity and Side Effects	Reference Study for Transarterial Use	Reference Study for Colorectal Liver Metastases
Bevacizumab	15 mg/kg body weight	Colorectal cancer, lung cancer, breast cancer, ovarian cancer, renal cancer	Hypertension, fatigue, diarrhea, proteinuria, thromboemboli, hemorrhage, bowel perforation	Burkhardt et al,[24] 2012	Glimelius et al,[39] 2012
Carboplatin	300 mg/m^2 body surface	Lung cancer, breast cancer, ovarian cancer, testicular cancer	Nausea and vomitus, tinnitus, allergy, abdominal pain, diarrhea, constipation, neurotoxicity, bone marrow suppression	Barletta et al,[40] 2006	Shimonov et al,[41] 2005
Caelyx (liposomal doxorubicin)	30 mg/m^2 body surface	See doxorubicin	See doxorubicin	Gonzalez Cao et al,[42] 2006	Moroney et al,[43] 2012
Cetuximab	100 mg/m^2 body surface	Colorectal cancer, head and neck cancer	Acnelike skin reaction, pruritus, hypomagnesemia, fever, shivering, vertigo, dyspnea	Rajappa et al,[23] 2010	Glimelius et al,[39] 2012
Cisplatin	100 mg/m^2 body surface	Head and neck cancer, lung cancer, ovarian cancer, cervix carcinoma, chorion carcinoma, testicular cancer, bladder cancer	Bone marrow suppression, anemia, hyperuremia, fever, heart arrhythmia, dyspnea, pneumonia, allergy	Mancini et al,[44] 2003	Gruber-Routh et al,[37] 2014
Doxorubicin	50 mg/m^2 body surface	Lung cancer, breast cancer, ovarian cancer, lymphoma	Bone marrow suppression, nephrotoxicity, cardiotoxicity,[a] skin ulceration	Liu et al,[45] 2015	Albert et al,[36] 2011
Docetaxel	75 mg/m^2 body surface	Head and neck cancer, lung cancer, breast cancer, ovarian cancer, prostate cancer, gastric cancer	Bone marrow suppression, fever, neurotoxicity, diarrhea, alopecia, hepatotoxicity, heart arrhythmia	Nakanishi et al,[46] 2012	Seki & Hori,[47] 2011

Epirubicin	75 mg/m^2 body surface	Lung cancer, breast cancer, ovarian cancer, gastric cancer, bladder cancer, lymphoma, sarcoma	Bone marrow suppression, alopecia, stomatitis, abdominal pain, nausea, and vomitus, diarrhea, anorexia	Tawada et al,[48] 2015	Fiorentini et al,[49] 2004
Fotemustin	100 mg/m^2 body surface	Melanoma, lymphoma	Bone marrow suppression, fatigue, nausea, vomitus, and alopecia	Edelhauser et al,[50] 2012	Hartmann et al,[51] 1997
Gemcitabine	1000 mg/m^2 body surface	Lung cancer breast cancer, ovarian cancer, pancreatic cancer, cholangiocellular carcinoma, sarcoma	Bone marrow suppression skin reaction, alopecia, stomatitis, hepatotoxicity, neurotoxicity, nephrotoxicity	Vogl et al,[52] 2008	Gruber-Routh et al,[37] 2014
Irinotecan	200 mg/m^2 body surface	Lung cancer, cervix carcinoma, esophagus cancer, gastric cancer, pancreatic cancer, cholangiocellular carcinoma, sarcoma	Bradycardia, lacrimation flush, diarrhea, hyperhidrosis, bone marrow suppression alopecia, nephrotoxicity, hepatotoxicity	Tsuchiya et al,[29] 2007	Gruber-Routh et al,[37] 2014
Mitomycin C	10 mg/m^2 body surface	Colorectal cancer, head and neck cancer, lung cancer, breast cancer, cervix carcinoma, esophagus cancer, gastric cancer, pancreatic cancer, hepatocellular carcinoma, bladder cancer	Skin necrosis, lung fibrosis, nephrotoxicity, bone marrow suppression, skin reaction, nausea and vomitus, cardiotoxicity	Vogl et al,[52] 2008	—
Mitoxantrone	14 mg/m^2 body surface	Breast cancer, prostate cancer, lymphoma, multiple sclerosis	Nausea and vomitus, anorexia, alopecia, stomatitis, bone	Boulin et al,[53] 2011	Link et al,[54] 2001

(*continued on next page*)

Table 2
(*continued*)

Type	Maximum Single Dose	Major Indications	Major Toxicity and Side Effects	Reference Study for Transarterial Use	Reference Study for Colorectal Liver Metastases
			marrow suppression, cardiotoxicity		
Oxaliplatin	660–80 mg/m^2 body surface	Colorectal cancer	Diarrhea, nausea and vomitus, bone marrow suppression, stomatitis, nephrotoxicity, neurotoxicity	Chen et al,[55] 2014	Nordlinger et al,[15] 2008
Paclitaxel	175 mg/m^2 body surface	Lung cancer (non-small cell lung cancer), breast cancer, ovarian cancer, prostate cancer	Bone marrow suppression, neurotoxicity, myalgia, alopecia, diarrhea nausea and vomitus	Koga et al,[56] 2003	Tsimberidou et al,[57] 2011

According to the guidelines, chemotherapeutic standards in the different lines for CLM include FOLFOX (1. folin acid [=leucovorin], 2. 5-FU, and 3. Oxaliplatin), FOLFIRI (1. folin acid [=leucovorin], 2. 5-FU, and 3. irinotecan), FOLFOXIRI (1. folin acid [=leucovorin], 2. 5-FU, 3. oxaliplatin, and 4. Irinotecan), FOLFIRINOX (1. folin acid [=leucovorin], 2. 5-FU, 3. irinotecan, and 4. oxaliplatin), Xelox (1. capectitabine [Xeloda; Roche, Basel, Switzerland] and 2. Oxaliplatin) and XELIRI (1. capectitabine [Xeloda; Roche] and 2. irinotecan); molecular substances are frequently used; the anti-EGFR antibodies Cetuximab (Erbitux; Imclone Systems, Bristol-Meyers Squibb, New York, NY, USA) and panitumumab (Vectibix; Amgen, Thousand Oaks, CA, USA) to block the growth receptor cascade as well as the anti-VEGF antibodies bevacizumab (Avastin; Roche) and regorafenib (Stivarga; Bayer, Berlin, Germany) to block neoangiogenes. For CLM, all relevant chemotherapeutics and molecular substances are available either for transarterial use (Oxaliplatin and irinotecan as well as Cetuximab [Erbitux; Imclone Systems, Bristol-Meyers Squibb]) and antibodies bevacizumab (Avastin; Roche) or for oral use (leucovorin, 5-FU, capecitabine (Xeloda; Roche) and the anti-VEGF antibody regorafenib (Stivarga; Bayer) (see also **Tables 4** and **5**).

[a] Dexrazoxane can used as cardioprotective medication in palliative patients.

Data from Refs.[15,23,24,29,36,37,39–57]

Table 3
Embolic agents used for hepatic arterial therapy

Product	Material	Type of HAT (cTACE, DSM-TACE, DEB-TACE, Y-90)	Sizes (μm)
Bead block (BTG, London, UK)	PVA	cTACE	100–300 or 300–500
Contour-SE (Boston Scientific, Marlborough, MA, USA)	PVA	cTACE	45–15, 150–250, or 250–355
DC Bead (BTG)	PVA loaded with irinotecan or doxocubucin	HAT-DEB	≈75, 100–300, 30–500
EmboCept S (PharmaCept)	Starch	DSM-DEB	≈50
EmboSphere (Merit Medical, South Jordan, UT, USA)	Tris-acryl gelatin	cTACE	40–120,100–300, or 300–500
Embozene Microspheres (CeloNova BioSciences, San Antonio, TX, USA)	Hydrogel core with a biocompatible nonocoat consisting of Polyzene-F	cTACE	40, 785, 100, 250, or 500
Gelatine sponge (Spongostan; Johnson & Johnson, New Brunswick, NJ, USA)	Gelatin	cTACE	Dependent on its formulation (pieces of ≈500 m, ≈1000, or ≈2000)
Gelfoam (Pfizer, New York, NY, USA)	Gelatin powder	cTACE	≈50
HepaSphere (Merit Medical)	PVA loaded with irinotecan or doxocubucin	HAT-DEB	30–60, 50–100, 100–150, or 150–200
Lipiodol (Laboratoire Guerbet, Aulnay-sous-Bois, France)	Iodized poppy seed oil	cTACE	Dependent on its formulation (droplets of 15–200)
LifePearl (Terumo, Tokyo, Japan)	Polyethylene glycol with sulfonide bonding loaded with irinotecan or doxocubucin	HAT-DEB	100, 200, or 300
PVA (Cook, Bloomington, IN, USA)	PVA	cTACE	90–180, 180–300, or 300–500
Spherex (Pharmacia AB, Stockholm, Sweden)	Starch	DSM-TACE	≈40
TANDEM (CeloNova BioSciences)	Hydrogel core with a biocompatible nonocoat consisting of Polyzene-F loaded with irinotecan or doxocubicin	HAT-DEB	40, 75, or 100
TheraSphere (Biocompatibles UK, Surrey, UK)	Y-90 impregnated glass	Y-90 radioembolization	20–30
SIR-Spheres (Sirtex Medical, Woburn, MA, USA)	Y-90 impregnated resin	Y-90 Radioembolization	20–60

is used for selective targeting of either the right or the left lobe of the liver.[60,61,63] Diagnostic angiography and intraprocedural cone-beam CT can help delineate the anatomy of all tumor-feeding arteries and allow operators to navigate the microcatheter accordingly. Catheter location is confirmed intraprocedurally using fluoroscopy. The selection of the adequate chemoembolics is another key and depends on several parameters (see later discussion).

After HAT-DEB, patients are monitored for treatment effect and disease recurrence through the use of clinical examination, blood tests, and contrast-enhanced imaging. Subsequent HAT-DEB treatments are commonly required and should be scheduled in conjunction with the off-week of the patient's systemic therapy, usually 4 to 6 weeks, with exact timing based on patient tolerance to combined therapy. Commonly, the right lobe is treated twice and the left lobe is treated once (over a 10- to 12-week time interval) before repeat response imaging is obtained. Official recommendations such as the Standards of Practice Guidelines of the Cardiovascular and Interventional Radiological Society of Europe can help to further standardize HAT-DEB for CLM.[64]

Technical Success, Complications, and Adverse Effects

In key studies of HAT-DEB for CLM, technical success—successful catheterization with subsequent selective/superselective deposition of chemoembolic agents within the target region—is close to 100%. Dissection or thrombosis of the hepatic artery is extremely rare.[20] Temporary vasospasm during catheterization is common but can be treated effectively with vasodilators (eg, repetitive transarterial bolus injections of 0.25 mg nitroglycerin). Arterioportal and arteriovenous shunts should be occluded to avoid the risk for nontarget embolization. After one or more HAT-DEB cycles, the chemoembolics can alter the larger tumor-feeding arteries. Very small microspheres (eg, irinotecan-loaded microspheres with a diameter of 40 $\pm$ 10 μm) can then be used to embolize the diffuse tumor vasculature together with protective temporary embolization of the nontarget liver tissue using DSMs if necessary.[65]

The "post-embolization syndrome," a relatively frequent side effect of HAT-DEB, comprises one or more of the following: fatigue, nausea, vomiting, mild fever, and laboratory values indicative of tumor necrosis. A recent review compared relevant toxicities of HAT-DEB, cTACE, CTx, and hepatic artery infusion (HAI).[20] For HAT-DEB, cited toxicities were nausea/vomiting (2%–55%), hypertension (4%–80%), liver dysfunction/failure (6%), cholecystitis (1%), gastritis (1%), anorexia (3%), abdominal pain (0%–57%), hematologic toxicity (9%–90%), fatigue (60%), and alopecia (5%–35%). For cTACE, toxicities comprised nausea/vomiting (18%–83%), fever (13%–83%), fatigue (24%–60%), abdominal pain (82%–100%), liver dysfunction/failure (13%–33%), gastritis (17%), neurotoxicity (45%), diarrhea (9%–31%), hematologic toxicity (13%–33%), and renal failure (4%). Finally, for CTx and HAI, cited toxicities were chemical hepatitis (7%–15% and 4%–79%, respectively), biliary sclerosis (not reported [NR] and 4% to 21%, respectively), peptic/duodenal ulceration (0%–3% and 0%–17%, respectively), gastritis/duodenitis (1%–7% and 1%–21%, respectively), diarrhea (16%–70% and 1%–44%, respectively), nausea/vomitus (35%–46% and 21%–61%, respectively), and stomatitis (14%–87% and 0%–76%, respectively).

Major complications of HAT-DEB such as liver abscess and tumor rupture are rare. Results of nontarget embolization (eg, pancreatitis or cholecystitis) can be avoided by sufficient evaluation of the arterial anatomy (eg, by using high-resolution angiography or intraprocedural cone-beam CT) and by using accepted hepatic embolization techniques (eg, flow-mediated embolization or balloon protection).[25,58] In experienced centers, the overall major and minor complication rates during and after HAT-DEB

are generally very low.[25–27,58] The procedure can be regarded as safe and well-tolerated provided standard catheterization and modern imaging techniques are used and the appropriate perioperative supporting medications are consistently administered.

Oncologic Outcomes

To assess the reported outcomes of HAT in patients with CLM, the authors reviewed articles describing HAT-DEB for CLM (search strategy: MEDLINE = database, "drug eluting beads + colorectal liver metastases" = search term for primary selections, cross references for additional selections). The original studies identified along with their relevant characteristics and disease-free and OS figures are detailed in **Table 4**. In summary, HAT-DEB for CLM is usually performed after failure of at least one and, more often, more systemic and/or surgical therapies. Otherwise, it is performed concomitantly with systemic therapy or in the perioperative period after hepatic resection. HAT-DEB regimens can produce a tumor response rate of 89%, a progression-free survival (PFS) rate of 13.6 months, and an OS of greater than 28 months.

Since 2011, several review articles addressing HAT-DEB for CLM have been published.[13,20,26,27,78–81] Some investigators emphasize an increased survival benefit and conclude that HAT-DEB should be implemented earlier in treatment algorithms for CLM, namely, after patients fail first- and second-line systemic therapy.[13] Others, however, state that the use of HAT-DEB cannot be definitively recommended for unresectable CLM because of the lack of prospective, randomized trials that would allow fair comparison with systemic regimens.[26] Regardless of their recommendations, all investigators acknowledge the appeal of evolving HAT-DEB techniques but recognize the lack of prospective clinical data from randomized trials.[4,10,26–29,38,58] They also agree that the safety and toxicity profile of HAT-DEB are comparable to or better than that of salvage CTx.

In terms of oncologic long-term outcomes, however, the optimal timing and utilization of HAT-DEB remain unclear. Thus, physicians should work toward standardization of HAT-DEB methodology. Finally, further investigations should examine the effect of earlier implementation of HAT-DEB in treatment algorithms as opposed to using such therapy only after failure of multiple surgical or systemic therapies.

Hepatic Arterial Therapy in Combination with Systemic Chemotherapy and/or Surgery

Few studies have reported outcomes of patients with CLM after HAT-DEB in combination with surgical resection. In the 1990s, Ceelen and colleagues[30] performed the only controlled trial with cTACE before resection. Fourteen patients underwent preoperative cTACE, whereas 9 patients were treated with partial hepatectomy alone. Reported OS and tumor recurrence rates were 93% and 8% (mean follow-up 15.5 months) versus 67% and 67% (mean follow-up 17.5 months), respectively. In this context, cTACE was *not* associated with increased operating time, transfusion requirement, or perioperative complication rates. The investigators concluded that preoperative cTACE reduces 12-month recurrence rates after curative liver resection and may improve OS.

Jones and colleagues[82] published 2 studies examining the radiologic-pathologic correlation of resection specimens in patients who underwent HAT-DEB before surgical resection. In the first study, a case-control series, 3 patients were treated with HAT-DEB (DEBIRI; 200 mg irinotecan loaded in a particle volume of 2 mL [particle size of 100–300 μm; DC Bead; BTG, London, UK]). Pathologic analysis of the surgical specimen demonstrated 0% tumor viability for all targeted liver metastases.

Table 4
Original studies of safety and efficacy of hepatic arterial drug-eluting bead therapy for colorectal liver metastases

Reference	Patients (n)	Therapy Stage (1st Line, 2nd Line, 3rd Line, Beyond 3rd Line)	Chemoembolics (Embolic Agents + Chemotherapeutics)	Median Follow-Up (mo)	Progression-free Survival (mo)	Median OS (mo)
Aliberti et al,[66] 2006	10	NR	DEBIRI (100 mg irinotecan) every 3 wk	NR	NR	NR
Martin et al,[60] 2009	30	2nd line	DEBs (100–700 μm)	9	NR	NR
Martin et al,[61] 2009	55	2nd line	DEBs (100–900 μm)	18	6.5	11.3
Martin et al,[58] 2010	84	2nd line	DEBs (100–700 μm)	NR	NR	NR
Martin et al,[67] 2011	55	2nd line	DEBs (100–700 μm)	18	11	19
Aliberti et al,[68] 2011	82	2nd line	DEBIRI	29	8	25
Fiorentini et al,[69] 2012	36 38[a]	NR	DEBIRI FOLFIRI	NR	7 4	22 15
Martin et al,[70] 2012	10	During the off week of FOLFOX	DEBIRI (100 mg irinotecan, 100–300 μm)	NR	NR	15.2
Jones et al,[71] 2013	22	Easily resectable CLM were treated with TACE 4 wk before resection	DEBIRI	22	13.6	NR
Eichler et al,[72] 2012	11	2nd line	DEBIRI (100–500 μm)	2.7	5.1	NR
Jones et al,[73] 2013	10	NR	DEBIRI (200 mg irinotecan) as part of PARAGON II	NR	NR	NR
Narayanan et al,[74] 2013	28	NR	DEBIRI	6.9	4	13.3
Huppert et al,[75] 2014	29	Beyond 2nd line	DEBIRI (35–400 mg irinotecan)	8	5	8
Akinwande et al,[76] 2014	22 149[b]	NR	DEBIRI + capecitabine DEBIRI only	10 —	7 9	22 13
Martin et al,[77] 2015	70	1st line	FOLFOX + DEBIRI FOLFOX alone	NR	17 15	13.7 16

[a] TACE versus systemic therapy.
[b] TACE 1 capecitabine versus TACE only.
Data from Refs.[58,60,61,66–77]

Nontargeted liver metastases as well as those detected at the time of operation also showed a response: 2 in the nontreated contralateral liver lobe (30% and 45% tumor viability, respectively) as well as 3 in the ipsilateral liver lobe (0%, 0%, and 60% tumor viability, respectively). Such data support the hypothesis that HAT-DEB has the potential to treat nontargeted liver metastases as well as micrometastases. In the second study, 22 patients were treated with HAT-DEB for 4 weeks before liver resection.[71] Disease-free survival was 13.6 months. However, the investigators noted that the Response Evaluation Criteria in Solid Tumors (RECIST) poorly predicted both pathologic response and clinical outcome. Accordingly, clinicians have discussed the use of different modalities for response assessment—cone-beam CT, angio-CT, hybrid-imaging, and biomarkers.

The use of systemic therapy in the preoperative setting to downstage CLM has been well established. The reported response rate and rate of conversion to resectability after CTx (FOLFOX, FOLFIRI, or FOLFOXIRI) range from 30% to 84% and 4% to 22%, respectively.[14,17,18,81,83] Patient selection and timing, dose, and type of the systemic therapy are relevant predictors of outcome. Kemeny and colleagues[84] recently demonstrated the potential of a strategy combining transarterial and systemic therapies. Fifty-three patients with primarily unresectable CLM (defined as at least one of the following: >5 liver metastases, bilobar disease, $\geq$6 involved segments) were treated with transarterial 5-fluoro-deoxyuridine and dexamethasone as HAI as well as systemic oxaliplatin and irinotecan. Tumor response rate was 92%, with 47% converting to resectability.

Akinwande and colleagues[76] subsequently described the combined use of HAT-DEB and oral systemic therapies. They showed that HAT-DEB plus Xeloda conferred a survival advantage (although not statistically significant) without additional toxicity compared with patients undergoing HAT-DEB only (22 vs 13 months). Their findings suggest that further studies should be undertaken to examine the effects of combining other oral agents for use in treatment of CLM (**Table 5**) with HAT-DEB.

Recently, Martin and colleagues[77] published the results of a randomized controlled trial assessing the safety and efficacy of DEBIRI with FOLFOX and bevacizumab versus FOLFOX and bevacizumab alone. They demonstrated no difference in toxicity between the FOLFOX-DEBIRI versus FOLFOX/bevacizumab treatment arms, a 6-month overall response rate of 76% versus 60% (P = .05), a conversion to resectability of 35% versus 16% (P = .05), and a median PFS of 15.3 versus 7.6 months. These findings suggest that DEBIRI represents a powerful adjunct to first-line CTx in patients with unresectable CLM.

YTTRIUM-90 RADIOEMBOLIZATION

Rationale and Patient Selection

Initially described in the 1980s, radioembolization represents another locoregional modality for the treatment of CLM.[85] Targeted arterial injection of Yttrium-90 (Y-90) microspheres results in embolization (and stasis) of tumor blood supply and the brachytherapy (localized delivery of radiation to hepatic tumors). As with patients being considered for HAT-DEB, candidates for Y-90 therapy should have greater than 3 months life expectancy and metastatic colorectal cancer with liver-predominant tumor burden. Absolute contraindications including the potential of greater than 30 Gy of radiation to the lung or the gastrointestinal tract can be avoided by manipulation of catheters. These possibilities are determined by a pretreatment macroaggregated albumin scan. Relative contraindications include poor baseline liver function, persistently elevated serum bilirubin, portal vein compromise, and prior hepatic radiation

Table 5
Original studies of safety and efficacy of Yttrium-90 radioembolization for colorectal liver metastases

Reference	Patients (n)	Therapy Stage (1st Line, 2nd Line, 3rd Line, >3rd Line)	Radioembolic Agent	Median Follow-Up (mo)	Median PFS (mo)	Median OS (mo)
Mantravadi et al,[85] 1982	15	NR	TheraSpheres	NR	NR	NR
Herba et al,[86] 2002	37	2nd line or beyond	TheraSpheres	8	NR	NR
Murthy et al,[87] 2007	10	3rd line or beyond	SIR-Spheres	5	NR	5.8
Sharma et al,[88] 2007	22	1st line	SIR-Spheres (+FOLFOX4)	NR	9.3	NR
Jakobs et al,[89] 2008	36	2nd line or beyond	SIR-Spheres	7.9	NR	10.5
Mulcahy et al,[90] 2009	72	2nd line or beyond	TheraSpheres	26.2	15.4	14.5
Nace et al,[91] 2011	51	3rd line	SIR-Spheres	NR	NR	10.2
Lam et al,[92] 2013	8	1st line or beyond	TheraSpheres SIR-Spheres	24.7	NR	3.1
Gunduz et al,[93] 2014	78	NR	SIR-Spheres	NR	4.4	10.1
Kalva et al,[94] 2014	45	2nd line or beyond	SIR-Spheres	4.9	NR	6.1
Abbott et al,[95] 2015	68	1st line or beyond	TheraSpheres	NR	NR	11.6

Data from Refs.[85–95]

therapy. As with HAT-DEB, pretreatment planning should also include CT or MRI, tumor markers, and serum chemistries. Furthermore, hepatic arterial flow characteristics should be carefully delineated using both preprocedural hepatic angiogram and intraprocedural fluoroscopy via percutaneously inserted intra-arterial catheters. Care should be taken to protect the gastrointestinal tract from inadvertent delivery of Y-90 by protective embolization of feeding blood vessels before radioembolization of the target hepatic lesions.[96,97]

Treatment and Toxicity

Y-90 treatments can be performed in 1 of 3 ways: whole liver, sequential (treating one hepatic lobe followed by the other), and lobar (treating only a single lobe of the liver). The optimal treatment varies based on disease burden and distribution, baseline hepatic function, and the patient's overall performance status. Projecting Y-90 microsphere activity is performed using either the (recommended) body surface area method or the empiric method. Dosing can be reduced by as much as 30% to account for impaired hepatic function or marginal hepatic reserve.[96,97]

Toxicity and complications of Y-90 treatment, much like DEBIRI, derive from the treatment itself (radiation), destruction of normal hepatocytes, and aberrant delivery of Y-90 microspheres. An analogue of post-embolization syndrome, post-radioembolization syndrome, consists of fatigue, nausea/vomiting, cachexia, and/or abdominal pain. Reported rates range from 20% to 70% and are rarely severe enough to require hospitalization.[98,99] In addition, although hepatic dysfunction occurs with 40% to 60% of Y-90 treatments, the vast majority is mild (grade I or II) and resolves within 30 days of treatment. Factors associated with persistent hepatic dysfunction are repeated radioembolization, prior external radiation therapy to the liver, and elevated pretreatment serum bilirubin and/or transaminases.[92,98] Other sequelae include biliary complications such as cholecystitis and cholangitis (more likely in patients with previous biliary procedures or surgeries), pancreatitis, and gastroenteritis.[100–102] These complications are infrequent (<5%–10%) and stem from aberrant deposition of microspheres into arterial communications with biliary, pancreatic, and/or enteric structures. They can be prevented through careful preprocedural assessment of each patient's arterial anatomy and prudent utilization of protective embolization before deposition of Y-90 beads.[98]

Efficacy and Response Evaluation

The safety and efficacy of Y-90 therapy have been demonstrated by several groups for treatment of chemotherapy-refractory CLM.[86,89,90,94,95,103–105] Specifically, Jakobs and colleagues[89] showed a median OS of 10.5 months with an adverse event rate of approximately 8%. The group also demonstrated an increased survival benefit in patients experiencing a decrease in carcinoembryonic antigen (CEA) level as well as a response on posttreatment imaging. More recently, Abbott and colleagues[95] assessed response in patients with varying hepatic burdens of disease and differing number of prior chemotherapy regimens. They showed a median OS of 11.6 months, with significantly greater median OS (19.6 months vs 3.4 months, $P<.001$) for patients with less than 25% hepatic disease burden (HBD) compared with those with greater than 25% HBD. On multivariate analysis, factors associated with decreased OS were age, 3 or more lines of prior chemotherapy, HBD greater than 25%, and higher CEA level.

As with DEBIRI, several groups have investigated the optimal means of assessing response to Y-90. In a 2007 report, Miller and colleagues[106] reviewed the imaging responses of CLM to Y-90 therapy using CT with various response criteria (World Health

Organization, RECIST, necrosis) as well as PET. They found that use of combined necrosis and RECIST criteria resulted in the highest response rate and also detected responses earlier than size criteria alone. PET also allowed for greater detection of treatment response than CT using RECIST or combined criteria. Finally, their statement that the use of PET in conjunction with CT imaging to detect recurrence earlier after treatment has been supported elsewhere in the literature, and PET should be considered a useful tool in posttreatment follow-up of patients treated with Y-90 therapy for CLM.[107]

Concomitant Use with Systemic Chemotherapy, Surgery

As with HAT-DEB, several investigators have examined the use of Y-90 with CTx.[88,108–110] Sharma and colleagues[88] combined Y-90 therapy with systemic FOLFOX4 in the treatment of 22 patients with CLM. Median PFS was 9.3 months, with a median hepatic-specific PFS of 12.3 months. In addition, 2 patients underwent conversion to resectability after treatment. De Souza and Daly[109] recently authored a case report describing the use of aflibercept (Aylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA) with FOLFIRI and Y-90 radioembolization. The patient underwent 2 discrete Y-90 treatments, first targeting the largest right lobe tumor and then targeting the left lobe tumor with re-treatment of the right lobe tumor. Based on the modified RECIST criteria, she demonstrated a partial response on CT and also experienced a decrease in her CEA levels. Currently, Gibbs and colleagues[108] and Dutton and colleagues[110] are conducting two randomized controlled trials assessing Y-90 therapy combined with FOLFOX6 ± bevacizumab versus FOLFOX6 ± bevacizumab alone and OxMdG with or without Y-90 therapy for treatment of unresectable CLM. Gibbs and colleagues[108] project an increase in median PFS from 9.4 to 12.5 months, similar to the data described by Sharma and colleagues.[88]

Several groups have also investigated the safety of hepatic resection after administration of Y-90. Whitney and colleagues[111] described 4 patients who underwent Y-90 therapy with good response and subsequently underwent hepatic resection with or without concomitant hepatic ablation. No patients demonstrated hepatic dysfunction or hepatic-specific recurrence after hepatectomy, and median survival was 2 years. Importantly, the investigators noted that the utility of preoperative Y-90 therapy lies not only in downstaging patients but also in assessing tumor biology, informing prognosis, and guiding therapy.

SUMMARY

The last several years have witnessed a significant increase in the use of HAT in patients with therapy-refractory CLM. The emergence of calibrated microspheres, together with improvements in DEB technology, has enabled physicians to perform both HAT-DEB and Y-90 embolization in a highly standardized and effective fashion. In most published studies, HAT-DEB and Y-90 are used either in the setting of controlled trials with patients who had failed first- or second-line chemotherapy or as salvage therapy for patients who had failed multiple previous surgical, ablative, and/or systemic therapies. The results of a randomized trial demonstrating the benefit of adding HAT-DEB to first-line CTx for unresectable CLM has recently been published. Currently, two similarly oriented trials for Y-90 are underway. Preoperatively, HAT may be used for tumor downsizing and conversion to resectability of CLM with minimal systemic toxicity and fewer adverse effects compared with systemic therapy. In addition, postoperatively, it can be used to prevent recurrence and improve OS. In nonsurgical candidates with liver-dominant metastases, palliative HAT in combination

with systemic therapy (chemotherapeutics and/or biologic agents) should be evaluated. Further randomized trials are required to better characterize the efficacy of HAT technologies for patients with CLM in the first, second, and third line and beyond.

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