Chapter 6
Liver Metastases of Other Indications

Michel Ducreux

6.1 Introduction

Locoregional treatment of liver metastases has been developed especially for tumors that give liver-limited metastases. For all the tumor types and especially for less usual that are presented in this chapter, the aim is to increase the amount of the drug delivered to the tumor and to decrease systemic toxicity.

Another potential interest of locoregional treatment of liver metastases seems to develop more active medical treatments in rather orphan tumors such as pancreatic cancer.

Even in diseases sensitive to several drugs or drug regimens, locoregional treatment could also prevent the appearance of resistance to systemic treatment (pancreatic carcinoma, breast cancer).

M. Ducreux
Gastrointestinal Cancer Unit, Department of Medical Oncology, Université Paris Saclay, Paris, France
e-mail: Michel.ducreux@gustaveroussy.fr

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In aggressive diseases such as pancreatic carcinoma and melanoma, it is obvious that the indications of locoregional treatment directed to the liver should not be proposed if there is any suspicion of extrahepatic disease. This requirement is not mandatory in tumors such as breast carcinoma in which the prognosis may be linked to liver involvement. In these tumors, liver locoregional treatment could be at least considered even if there is extrahepatic disease when the liver metastases are able to rapidly shorten the survival of the patients.

Some of the inclusion criteria for arterial liver treatment are common to all these rare indications:

- Tumor mass <50% liver volume
- Normal vessel system, which allows the placement of the catheter into the A. gastroduodenalis or A. hepatica propria
- Open portal vein
- No ascites

Some of the inclusion criteria are true for melanoma and breast carcinoma but not for pancreatic adenocarcinoma because liver surgery is approximately never considered in this disease:

- Nonresectable tumors
- Relapsed metastases after liver resection
- Metastases in both lobs
- General contraindications for operation
- Refusal of operation by patient

These unusual indications clearly need a multidisciplinary discussion including oncologists, interventional radiologists, diagnostic radiologists, surgeons, and pathologists.

Treatment of metastases is always difficult especially when they are related to a very aggressive disease such as pancreatic carcinoma or uveal melanoma. On the other hand, 80–90% of metastases due to these two cancers appear in the liver. These two arguments gave a strong rationale for the use of HAI or chemoembolization in adjuvant setting.

6.2 Liver Metastases of Pancreatic Adenocarcinoma

6.2.1 Adjuvant Treatment

Beger et al. (1999) [1]

Concept	Resection + intra-arterial chemotherapy vs. resection alone
N	51
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	d1: 10 mg/m^2 mitoxantrone (over 1 h) d2–4: 170 mg/m^2 FA (over 10 min) + 600 mg/m^2 5-FU (over 2 h) d5: 60 mg/m^2 cisDDP (over 1 h)
Frequency	Every 4 weeks
Survival	23 mo vs. 11 mo R0 resection (at 4 years): 54 vs. 10%
Occurrence of hepatic metastases	Reduction to 17%
Toxicity	No severe local side effects
Conclusion	The results demonstrate that CAI is well tolerated, reduces the risk of liver metastasis, and increases the survival time of pancreatic cancer patients

d days, *mo* months

Cantore et al. (2006) [2]

Concept	Resection + intra-arterial chemotherapy +/− IV gemcitabine
N	47
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	5FU 750 mg/m^2, leucovorin 75 mg/m^2, epirubicin 45 mg/m^2, carboplatin 225 mg/m^2 (FLEC regimen)
Frequency	Every 3 weeks

Survival	Median disease-free survival, 16.9 months; median overall survival, 29.7 months
Occurrence of hepatic metastases	62% of recurrence
Toxicity	Main grade 3 toxicity related to HAI was only nausea/vomiting in 4% of the patients
Conclusion	FLEC regimen with or without gemcitabine is active with a very mild toxicity, and results are very encouraging in an adjuvant setting

Hayashibe et al. (2007) [3]

Concept	Resection + intra-arterial chemotherapy vs. resection alone (nonrandomized)
N	22
Access	Catheter via A. femoralis in proper hepatic artery
Therapy	5FU 500 mg/m^2 180 min infusion + cisplatin 10 mg/m^2
Frequency	Weekly "as much as possible"
Survival	15.8 months vs. 13.4 months NS
Occurrence of hepatic metastases	33% in the treated group vs. 54% in the control group
Toxicity	No severe local side effects
Conclusion	In patients with pancreatic cancer who underwent the curative operation, the intra-arterial adjuvant chemotherapy had the tendency to suppress the rate of liver metastasis and improve cumulative survival

6.2.2 Metastatic Disease

Homma and Niitsu (2002) [4]

Concept	Hepatic arterial infusion
N	31
Access	Catheter into A. femoralis to celiac artery

Therapy	20 mg/m^2 cisDDP (d1, 3, 5) + 500 mg/m^2 5-FU (d1–7)
Frequency	Every 4 weeks
Survival	1 year, 2 years, 3 years: 67, 31, 14% Median survival: 16 months
Toxicity	Cytopenia (grade 2): $N = 11$, transient nausea, mild anorexia
Conclusion	In patients with stage IV advanced pancreatic carcinoma, arterial infusion chemotherapy after hemodynamic change was found to be effective against both primary tumors and metastatic liver lesions

Vogl et al. (2006) [5]

Concept	Intra-arterial dose finding of gemcitabine +/− starch microspheres
N	24
Access	Catheter into A. femoralis placed in the truncus coeliacus
Therapy	HAI: Initial dose, 1000 mg/m^2 (d1 + d8) every 2 weeks (max. 6 cycles); dose steps, 200 mg/m^2 (till MTD) TACE: Initial dose, HAI-MTD—1 dose step + microspheres
MTD	HAI: 1600 mg/m^2 TACE: 1800 mg/m^2
Time to progression	HAI: 4 months TACE: 7 months
Survival	Median survival: 9.1 months HAI: 14 months TACE: 20 months
Toxicity	Myelosuppression (grade 3)
Conclusion	This clinical study indicates that the intra-arterial application of gemcitabine with doses higher than the recommended 1000 mg/m^2 is well tolerated if combined with microspheres and yields respectable results in patients who do not respond to systemic chemotherapy

Heinrich et al. (2013) [6]

Concept	HAI + IV therapy
N	17
Access	Catheter into A. femoralis placed in the truncus coeliacus
Therapy	HAI: mitomycin C 8.5 mg/m^2 and gemcitabine 500 mg/m^2 d1, d22 IV: gemcitabine 500 mg/m^2 d8, d15
Response rates	24%
Survival	Median survival: 9.1 months Median progression-free survival: 4.6 months
Toxicity	Grade 3–4 hematological toxicity: 48.6% of the cycles
Conclusion	IV and IA treatment with gemcitabine combined with IA treatment with mitomycin C gives interesting treatment in refractory patients
Conclusion	FLEC regimen with or without gemcitabine is active with a very mild toxicity, and results are very encouraging in an adjuvant setting

Ikeda et al. (2007) [7]

Concept	HAI + IV therapy
N	33
Access	Port system (catheter into A. subclavia or right A. femoralis)
Therapy	IV: 1000 mg/m^2 gemcitabine (over 30 min) d1, 8, 15 HAI: 250 mg/m^2 5-FU d1–5
Frequency	Every 4 weeks
Response rates	PR: *N* = 8 (24%), PD: 9 (27%)
Survival	?
Toxicity	Leukopenia (grade 3), *N* = 8; thrombocytopenia, *N* = 6; non-hematologic (grade 3), *N* = 5
Conclusion	For patients with advanced pancreatic cancer, HAI with systemic chemotherapy appeared to be effective and may prolong survival

6.2.2.1 Randomized Studies

Cantore et al. (2003) [8]

Concept	Intra-arterial chemotherapy vs. IV gemcitabine
N	71 vs. 67
Access	Catheter via A. femoralis in truncus coeliacus
Therapy	5FU 1000 mg/m^2, leucovorin 100 mg/m^2, epirubicin 60 mg/m^2, carboplatin 300 mg/m^2 (FLEC regimen)
Frequency	Every 3 weeks
Response rate	14% for FLEC vs. 5.9% for gemcitabine (NS)
Survival	Median overall survival: 7.9 months in the FLEC group vs. 5.8 months in the gemcitabine group ($p = 0.13$)
Toxicity	Main grade 3 toxicity related to IAC was only nausea/vomiting in 4%; regarding gemcitabine, grade 3 toxicities were anemia 8%, leukopenia 8%, thrombocytopenia 17%, nausea/vomiting 4%

6.2.2.2 TACE

Azizi et al. (2011) [9]

Concept	TACE for liver metastases
N	32
Access	Femoral arterial access, advanced into the relevant segmental artery
Therapy	8 mg/m^2 MMC + 40 mg/m^2 cisDDP + 1000 mg/m^2 gemcitabine + Lipiodol + 200–450 mg DSM
Frequency	Every 4–8 weeks
Response rates	PR, $N = 3$ (9%); SD, $N = 23$ (72%); PD, $N = 6$ (19%)
Survival	Median survival: 16 months (SD, 20 months; PD, 5 months)
Toxicity	No major complications
Conclusion	Repetitive TACE resulted in a relevant response for the control of liver metastases of pancreatic cancer with respectable median survival time

6.2.3 Recommendations

Locoregional treatment of liver metastases of pancreatic adenocarcinoma remains a matter of research. It is conceptually interesting for the treatment of pancreatic carcinoma even if recent polychemotherapy has given interesting results (FOLFIRINOX, gemcitabine + nab-paclitaxel). In adjuvant setting the data are scarce, but considering the high level of liver recurrence after surgical excision of pancreatic cancer and even if systemic treatment has given some hope, it could be considered in future trials.

6.3 Liver Metastases of Melanoma

6.3.1 Hepatic Arterial Infusion

Becker et al. (2002) [10]

Concept	HAI or IV of fotemustine + SC IL-2 + IFN
N	48
Inclusion criteria	Liver and extrahepatic metastases
Therapy	d1: IA 100 mg/m^2 fotemustine (over 60 min) or IV 100 mg/m^2 fotemustine (over 15 min) d31–33: SC 10×10^6 IU/m^2 IL-2 (2×/d) d36, 38, 40: SC 10×10^6 IU/m^2 IFN + SC 5×10^6 IU/m^2 IL-2
Response rates	RR: 15% ($N = 7$) (5 from the HAI group) HAI vs. IV: 22 vs. 8% CR, $N = 1$; PR, $N = 6$
Survival	8.5 months (HAI vs. IV: 369 vs. 349 d)
Toxicity	Thrombocytopenia, leucopenia (more prominent systemic side effects in the IV group)

Conclusions	Although objective responses were more frequent within the cohort receiving intra-arterial fotemustine, this difference did not translate into a significant benefit in overall survival. Of note, this overall survival is much longer than that repeatedly reported for stage IV uveal melanoma not treated with fotemustine, suggesting a therapeutic activity of this cytostatic drug even after systemic administration

Peters et al. (2006) [11]

Concept	HAI (retrospective study)
N	101
Inclusion criteria	Chemotherapeutic naive patients
Therapy	100 mg/m^2 fotemustine (over 4 h) Every 4 weeks
Response rates	RR: 36% CR: *N* = 15; PR: *N* = 21; SD: *N* = 48 TtP: 9 months
Survival	Median survival: 15 months 1 year, 2 years, 3 years: 67, 29, 12%
Toxicity	Grades 3 and 4, 11% (mainly hematoxicity); grade 2, the grade toxicities seen in these patients were related to hematologic toxicity Complications with catheters: *N* = 21 (thrombosis, dislocation, obstruction, leakage)
Conclusions	Locoregional treatment with fotemustine is well tolerated and seems to improve outcome of this poor prognosis patient population

Siegel et al. (2007) [12]

Concept	HAI (retrospective study)
N	30 (18 uveal)
Inclusion criteria	Liver-limited disease
Therapy	100 mg/m^2 fotemustine (over 4 h) Every 4 weeks

Response rates	RR: 30% PR, $N = 9$; SD, $N = 10$ TtP: 9 months
Survival	Median survival: 14 months 1 year, 2 years, 3 years: 67, 29, 12%
Toxicity	≥ grade 3 thrombocytopenia/30%; ≥ grade 3 neutropenia, 7%
Conclusions	Hepatic arterial fotemustine chemotherapy was well tolerated. Meaningful response and survival rates were achieved in ocular as well as cutaneous melanoma

Voelter et al. (2008) [13]

Concept	HAI (prospective study, historical control)
N	22
Inclusion criteria	High risk of liver metastases patients
Therapy	100 mg/m^2 fotemustine (over 4 h) Every 3 weeks
Response	NA—adjuvant treatment
Survival	Median survival: 9 years vs. 7.4 years for control group 5-year survival: 75% vs. 56%
Toxicity	50% grade 3–4 hepatotoxicity including one patient with cholangitis 8 years later
Conclusions	Although these data suggest a survival benefit, it was not statistically significant. Confirming such a benefit would require a large, internationally coordinated, prospective randomized trial

Farolfi et al. (2011) [14]

Concept	HAI
N	23
Inclusion criteria	Patients after treatment failure of systemic therapy for hepatic metastases from melanoma (uveal)
Therapy	100 mg/m^2 fotemustine or 50 mg cisDDP Every 2–4 weeks

Response rates	Uveal melanoma ($n = 18$) RR: 17% Disease control rate (PR + SD): 72%
Survival	Median PFS: 6.2 months Median survival: 21 months
Toxicity	No grade 4 toxicity Grade 3: fever in the absence of a detectable focus for 3 days ($N = 3$), splenic infarction ($N = 1$) treated conservatively, thrombocytopenia ($N = 1$), and gastric ulcer ($N = 1$)
Conclusions	IAC with fotemustine is well tolerated and is a valid choice for patients with a poor prognosis since median survival rates are among the longest reported

Heusner et al. (2011) [15]

Concept	HAI (retrospective analysis)
N	61
Inclusion criteria	Liver and extrahepatic metastases
Therapy	Melphalan or melphalan + fotemustine, dacarbazine, MMC, doxorubicin, or gemcitabine Every 4 weeks
Response rates	At four sessions: PR, 30%; SD, 15%; PD, 55% At six sessions: PR, 19%; SD, 57%; PD, 24%
Survival	Median survival: 10 months Extrahepatic vs. hepatic metastases only: 6 vs. 14 months ≤ vs. >9 metastases: 17 vs. 9 months
Toxicity	Liver failure in one patient (0.4%), thrombocytopenia (20%), leucopenia (16%)
Conclusions	Intra-arterial sequential hepatic chemoperfusion offers a minimally invasive treatment in patients with hepatic uveal melanoma metastases with good survival times and an acceptable major complication rate

6.3.2 TACE

6.3.2.1 Standard TACE

Mavligit et al. (1988) [16]

Concept	TACE
N	30
Inclusion criteria	Liver metastases
Therapy	Chemoembolization with cisplatin and polyvinyl sponge
Response rates	RR: 46% CR, *N* = 1; PR, *N* = 13
Survival	11 months
Toxicity	Primarily severe upper right quadrant abdominal pain, transient paralytic ileus, and nonicteric hepatitis
Conclusions	Hepatic arterial chemoembolization provided effective palliation, with good-quality survival among 46% of patients with ocular melanoma metastatic to the liver

Patel et al. (2005) [17]

Concept	TACE
N	24
Inclusion criteria	Liver metastases
Therapy	Chemoembolization with BCNU dissolved in ethiodized oil, Gelfoam
Response rates	RR: 21% CR, *N* = 1; PR, *N* = 4
Survival	5.2 months
Toxicity	Grade 3 or 4 toxicity was experienced by eight patients (two hepatic vein thromboses and one portal vein thrombosis, one patient had a partial splenic infarct); one patient without prior treatment developed grade 3 thrombocytopenia that improved to grade 1 within 2 weeks, one renal insufficiency, two liver failures

Conclusions	Chemoembolization with BCNU is a useful palliative treatment for the control of hepatic metastases in uveal melanoma patients. However, progression in extrahepatic sites after stabilization of hepatic metastases requires further improvement in the therapeutic approach to this disease

Sato et al. (2008) [18]

Concept	TACE
N	31
Inclusion criteria	Liver metastases
Therapy	Chemoembolization with granulocyte-macrophage colony-stimulating factor, emulsified in ethiodized oil, Gelfoam
Response rates	RR: 32% CR, *N* = 2; PR, *N* = 8
Survival	14.4 months
Toxicity	Mild. MTD was not reached up to the dose level of 2000 mg, and there were no treatment-related deaths
Conclusions	Immunoembolization with GM-CSF is safe and feasible in patients with hepatic metastasis from primary uveal melanoma. Encouraging preliminary efficacy and safety results warrant additional clinical study in metastatic uveal melanoma

Schuster et al. (2010) [19]

Concept	TACE
N	25
Inclusion criteria	After treatment failure of systemic therapy for hepatic metastases from uveal melanoma
Therapy	100 mg/m^2 fotemustine + max 900 mg DSM or 50 mg cisDDP + max 900 mg DSM Every 2–4 weeks
Response rates	RR: 16% PR, *N* = 4; SD, *N* = 14 Disease control rate (PR + SD): 72%

Survival	Median PFS: 3 months (no significant difference between the fotemustine ($n = 16$) and the cisplatin ($n = 9$) group) Median survival: 5 months
Toxicity	No grade 4 toxicity Grade 3: fever in the absence of a detectable focus for 3 days ($N = 3$), splenic infarction ($N = 1$) treated conservatively, thrombocytopenia ($N = 1$), and gastric ulcer ($N = 1$)
Conclusions	TACE is well tolerated and effective in pretreated patients with liver metastases from uveal melanoma. TACE should further be evaluated as first-line therapy in prospective randomized clinical trials

Gupta et al. (2010) [20]

Concept	TACE
N	125
Inclusion criteria	Liver metastases of uveal melanoma
Therapy	Chemoembolization
Response rates	Partial response: 27%
	Disease stabilization: 65%
Survival	Median overall survival: 6.7 months
	Median disease-free survival: 3.8 months
	Multivariate analysis: >75% liver involvement and high lactate dehydrogenase levels were associated with short overall survival
	Median survival >75%: 2.4 months
Toxicity	???
Conclusions	TACE is an active treatment of liver metastases of uveal melanoma

Huppert et al. (2010) [21]

Concept	TACE
N	14
Inclusion criteria	Liver metastases of uveal melanoma
Therapy	Chemoembolization with continuous infusion of cisplatin

Response rates	Partial response: 57% Disease stabilization: 29%
Survival	Median overall survival: 11.5 months Median time to progression: 8.5 months <25% liver involvement: median overall survival 17 months
Toxicity	???
Conclusions	TACE of liver metastases from uveal melanoma is well tolerated and may prolong survival in patients with limited tumor extension

Ahrar et al. (2011) [22]

Concept	TACE
N	42
Inclusion criteria	Liver metastases of cutaneous melanoma
Therapy	Chemoembolization
Response rates	Partial response: 38.9% Disease stabilization: 47.2%
Survival	Median overall survival: 7 months Median disease-free survival: 6 months Significant predictors of OS: patient's age, LDH levels, type of treatment, number of extrahepatic metastatic sites, and response to therapy
Toxicity	
Conclusions	TACE is an active treatment of liver metastases of cutaneous melanoma

Edelhauser et al. (2012) [23]

Concept	TACE
N	21
Inclusion criteria	Patients with liver metastases from uveal melanoma
Therapy	50 mg/m^2 fotemustine + Lipiodol every 6–8 weeks
Response rates	RR: 14% Disease control rate (PR + SD): 72%
Survival	Median survival: 28.7 months

Toxicity	Minor side effects: postembolization syndrome with fever 19%, pain 14%, nausea 24%
Conclusions	TACE with fotemustine of hepatic metastases from uveal melanoma with fotemustine was well tolerated and gave interesting results in terms of response rate and overall survival

Valsecchi et al. (2015) [24]

Concept	Embolization with or without granulocyte-macrophage colony-stimulating factor (GM-CSF) (immunoembolization)
N	Randomized phase II trial Immunoembolization = 25 (IE) Bland embolization = 27 (BE)
Inclusion criteria	Patients with liver metastases from uveal melanoma
Therapy	GM-CSF 2000 μg + Lipiodol or normal saline solution + Lipiodol Followed by embolization with gelatin sponge
Response rates	RR: 21% IE group versus 17% BE group Disease control rate (PR + SD): 68% IE group vs. 81% BE group
Survival	Median survival: 21.5 months IE group, 17.2 BE group
Toxicity	No difference between the two groups. Most common side effects: transient increases of hepatic enzyme levels and liver pain
Conclusions	Immunoembolization induced more robust inflammatory responses, which correlated with the delayed progression of extrahepatic metastases

6.3.2.2 TACE with New Embolization Vectors

Firorentini et al. (2009) [25]

Concept	TACE with DC beads loaded with irinotecan (DEBIRI)
N	10
Inclusion criteria	Liver metastases

Therapy	Irinotecan 100–200 mg preloaded in 2–4 mL beads of 100–300/300–500 μm 15 TACE procedures, 5 patients had one procedure, 5 patients had 2 procedures
Response rates	Three patient reduction of 90%, three patient reduction of 80%, four patient reduction between 60 and 70%
Survival	Median survival: NA Eight patients alive at the time of writing; two patients with huge liver involvement died after 4 and 6 months due to rapid progression in the liver
Toxicity	No hematological toxicity or alopecia
Conclusions	Preliminary data but it seems that TACE adopting the new embolic material DC beads with irinotecan is highly effective in liver metastases from uveal melanoma

Valpione et al. (2015) [26]

Concept	TACE with DC beads loaded with irinotecan (DEBIRI) Retrospective analysis of a prospectively maintained database
N	58
Inclusion criteria	Liver metastases of uveal melanoma. First-line therapy
Therapy	DC beads loaded with irinotecan (DEBIRI) Every 4 weeks
Survival	Median survival TACE with DC beads:16.5 months Historical control: 12.2 months Better benefit in patients with liver involvement >50%
Toxicity	No severe toxicity
Conclusions	TACE using DC beads loaded with irinotecan is effective in liver metastases from uveal melanoma

6.3.3 Radioembolization

Gonsalves et al. (2010) [27]

Concept	Radioembolization with ^{90}Y spheres
N	32
Inclusion criteria	Liver metastases of uveal melanoma. Refractory patients
Therapy	^{90}Y spheres (SIRTEX)
Response rates	CR: 3% PR: 3% SD: 56%
Survival	Median overall survival: 10 months Progression-free survival: 4.7 months
Toxicity	Grade 3–4 hepatic toxicity, 12.5%; systemic toxicity, 28% grades 1–2
Conclusions	Interesting ratio efficacy/toxicity of radioembolization in refractory uveal melanoma

6.3.4 High-Dose Hepatic Arterial Infusion and Hemofiltration

Pingpank et al. (2005) [28]

Concept	High-dose liver infusion of melphalan + hemofiltration (PHP), phase I study
N	28. 10 with uveal melanoma
Inclusion criteria	Liver metastases of various malignancies
Therapy	Double-balloon inferior vena cava (IVC) catheter system. Infusion of melphalan (30 min) and hemoperfusion of the liver effluent with drug filtration cartridges (Delcath® system). First cohort of 12 patients 2 mg/kg, second cohort 3.5 mg/kg
Response rates	RR: 50%
Survival	14.4 months

Toxicity	67% grade 3–4 transient systemic toxicity
Conclusions	PHP with melphalan can be performed safely at an MTD of 3.0 mg/kg. Regional toxicity was minimal. Interesting activity has been observed even if it was not the main endpoint of this phase I trial

Hughes et al. (2016) [29]

Concept	High-dose liver infusion of melphalan + hemofiltration, phase III
N	44: percutaneous hepatic perfusion (PHP) 49: best alternative care (BAC), 28 crossovers to PHP
Inclusion criteria	Liver metastases of cutaneous and uveal melanoma
Therapy	Double-balloon inferior vena cava (IVC) catheter system. Infusion of melphalan (30 min) and hemoperfusion of the liver effluent with drug filtration cartridges (Delcath® system). Melphalan 3 mg/kg. Treatment every 4–8 weeks
Response rates	RR PHP: 36%
Survival	Median hepatic progression-free survival: 7.0 months PHP vs. 1.6 months BAC. Median overall progression-free survival: 5.4 months vs. 1.6 months Median overall survival: 10.6 months PHP vs. 10.0 months, NS
Toxicity	Any adverse events: 90%. 17.1% febrile neutropenia. Procedure-associated hypotension routinely noted
Conclusions	PHP with melphalan is a new treatment option for unresectable metastatic melanoma in the liver

6.3.5 Recommendations

Uveal melanoma metastases occur most commonly in the liver. Even if recent treatments have been proven to be effective in metastatic melanoma (ipilimumab, vemurafenib), it remains

very difficult to treat liver metastases of melanoma. This is particularly true for uveal melanoma which is able to specifically give limited liver metastases even very late after the treatment of the primary tumor. In this specific population, the role of immunotherapy seems less clear, and surgery remains the first choice in the treatment of these lesions. But surgery is frequently limited to one or two attempts of resection and then failed to control the disease due to its extension or the paucity of the remnant liver. In that setting, intra-arterial hepatic chemotherapy with fotemustine has given interesting results and should be considered in selected cases. Other options are TACE and PHP with high-dose melphalan, but there are less data to support this kind of treatment.

6.4 Liver Metastases of Breast Cancer

6.4.1 HAI

Cocconi et al. (2005) [30]

Concept	HAI
N	10
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapies	IA: 65 mg/m^2 (40–100 mg/m^2) docetaxel Every 3 weeks (max. 6 cycles)
Response rates	PR, 4/9; SD, 4/9
Survival	Median survival: 46 months
Toxicity	Hematological (grade 3), $N = 6$; non-hematological (grade 3), $N = 2$ (pain, asthenia)
Conclusions	The administration of docetaxel via the hepatic artery is feasible with a highly interesting response

Zhang et al. (2013) [31]

Concept	HAI
N	28
Inclusion criteria	Liver metastases
Therapy	Docetaxel 75 mg/m^2 and epiadriamycin 50 mg/m^2 every 3 weeks
Toxicity	No serious complications
Response rates	CR: 4% RR: 82%
Survival	None reported. 3 R0 liver surgery
Conclusion	Intra-arterial chemoinfusion is a safe and effective therapy, achieving downstaging in a relatively short period for locally advanced breast cancer

6.4.2 TACE

Giroux et al. (2004) [32]

Concept	Chemoembolization (retrospective analysis)
N	8
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	100 mg cisDDP + 50 mg doxorubicin + 10 MMC + Lipiodol + PVA Every 4 weeks (1–4 cycles)
Response rates	RR, 5/8; SD, 1/8
Survival	Mean survival: 49 months (from primary diagnosis); 20 months (from liver metastasis diagnosis); 6 months (from TACE)
Toxicity	No complications related to TACE
Conclusions	Chemoembolization stabilizes or improves the liver tumor burden, which may palliate symptoms, but most patients go on to develop other metastatic sites, which eventually lead to death

Li et al. (2005) [33]

Concept	TACE vs. systemic chemotherapy (retrospective comparison)
N	48 (28, 20)
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	TACE: 1000 mg 5-FU or FUDR + 40–60 mg cisDDP (infusion) followed by 40–60 mg doxorubicin + Lipiodol or Gelfoam IV: different anthracycline-based schedules or Taxotere + cisDDP Every 4 weeks
Response rates	RR (%): 35.7 vs. 7.1 (p <0.005)
Survival	Median survival: 28.0 vs. 18.0 months 1 year, 2 years, 3 years (%): 63, 30, 13 vs. 34, 11, 0
Toxicity	TACE: leuko-/thrombocytopenia (grades 1–2), elevation of liver enzymes (grades 1–2) IV: leuko−/thrombocytopenia (grades 1–4), elevation of liver enzymes (grades 1–2)
Conclusions	TACE treatment of liver metastases from breast cancer may prolong survival in certain patients. This approach offers new promise for the curative treatment of the patients with metastatic breast cancer

Vogl et al. (2010) [34]

Concept	TACE with two different schedules of chemotherapy
N	208
Inclusion criteria	Liver metastases
Therapy	8 mg/m^2 MMC + Lipiodol (n = 76) 1000 mg/m^2 gemcitabine + Lipiodol (n = 21) 8 mg/m^2 MMC + 1000 mg/m^2 gemcitabine + Lipiodol (n = 111) Embolization with starch microspheres
Response rates	RR 13% Stable disease: 36.5%

Survival	1 year, 2 years, 3 years survival of the whole group: 69, 40, 33% Median survival MMC: 13.3 months Gemcitabine: 11 months MMC + gemcitabine: 24.8 months
Conclusion	TACE is an optional therapy for treatment of liver metastases in breast cancer patients with better results from the combined chemotherapy protocol

Vogl et al. (2011) [35]

Concept	TACE with two different schedules followed by LITT
N	161
Inclusion criteria	Liver metastases after mastectomy
Therapy	8 mg/m^2 MMC + Lipiodol + 200–450 mg DSM ($N = 53$) or 8 mg/m^2 MMC + 1000 mg/m^2 gemcitabine + Lipiodol + 200–450 mg DSM ($N = 108$)
Response rates	After TACE: PR, 57%; SD, 43% Mean tumor reduction: MMC vs. MMC + gemcitabine, 27% vs. 27% After TACE + LITT: CR, 39%; PR, 5%; SD, 12%
Survival	Median survival: 33 months (5–101) 1 year, 2 years, 3 years, 5 years (%): 89, 56, 37, 13% MMC: 45 months (5–101) MMC + gemcitabine: 26 months (5–63) TtP: MMC vs. MMC + gemcitabine, 8 vs. 11 months
Toxicity	No or only few symptoms under TACE (mild): fatigue, abdominal pain, fever, nausea/vomiting
Conclusions	TACE can be used for sufficient downstaging of liver metastatic lesions of breast cancer to allow laser-induced thermotherapy. A combination of mitomycin C and gemcitabine seems to improve the reduction achieved with TACE

Duan et al. (2011) [36]

Concept	Comparison of TACE plus systemic chemotherapy vs. systemic chemotherapy alone
N	87 (44, 43)
Inclusion criteria	Liver metastases after mastectomy
Therapy	TACE: 5-FU or FUDR + cisDDP (infusion) followed by doxorubicin + Lipiodol or Gelfoam IV: different anthracycline- or taxane-based schedules (82%) or others Every 4 weeks (median: 6 cycles)
Response rates	RR (%): 59 vs. 35 (p <0.05) CR, 14 vs. 9%; PR, 12 vs. 6%
Survival	Median survival: 29 months (42 vs. 26 months) $p = 0.027$ 1 year, 2 years, 3 years (%): 63, 48, 28% (76, 67, 48 vs. 48, 30, 7%)
Toxicity	Leukopenia, 39 vs. 46%; hypochromia, 11 vs. 7%; thrombocytopenia, 9 vs. 14%; nausea/vomiting, 5 vs. 2%; impairment of liver function, 11 vs. 9%; abdominal pain in most of the TACE group of patients
Conclusions	The combined treatment of TACE and systemic chemotherapy may prolong survival for liver metastases in breast cancer after mastectomy

Eichler et al. (2013) [37]

Concept	TACE with gemcitabine
N	43
Inclusion criteria	Liver metastases
Therapy	Suspension of gemcitabine 1.200 mg/m^2, 2–10 mL/m^{2}of Lipiodol, and 5 mL of degradable starch microsphere (EmboCept) administered intra-arterially up to three times with a 4-week interval (n = 111)
Toxicity	Mild hematological toxicity: 20%. Grade 1/2 nausea/vomiting: 51%/5%. One case of Lipiodol encapsulation in the stomach. Full recovery in 1 day

Response rates	RR 7% Stable disease: 37%
Survival	Median progression-free survival: 3.3 months Median overall survival: 10.2 months
Conclusion	Transarterial chemoembolization with gemcitabine is well tolerated and provides an alternative treatment method for patients with liver metastases of breast cancer

6.4.3 TACE with New Vectors

Martin et al. (2012) [38]

Concept	TACE with doxorubicin-loaded drug-eluting beads (DEBDOX). Multicenter, prospective, open, noncontrolled repeat treatment registry
N	40 patients, 75 procedures
Inclusion criteria	Liver metastases under systemic chemotherapy
Therapy	Doxorubicin-loaded drug-eluting beads (DEBDOX)
Response rates	???
Survival	Median progression-free survival: 26 months Median overall survival: 47 months
Toxicity	13 grade 1 and 2 adverse events (17% of the procedures)
Conclusions	The treatment of hepatic metastasis from MBC using DEBDOX is an effective local therapy with very high response rates and a very safe toxicity profile

6.4.4 Radioembolization with (90)Y-Labeled Microspheres

Cianni et al. (2013) [39]

Concept	Radioembolization with (90)Y-labeled resin microspheres
N	52
Inclusion criteria	Inoperable and chemotherapy-refractory hepatic metastases

Therapy	(90)Y-labeled resin microspheres: median dose 1.9 GBq (range 0.33–2.71)
Response rates	RR: 56% SD: 35%
Survival	Median survival: 11.5 months 14.3 months in patients without extrahepatic disease, ECOG PS less than 1, less than 25% of hepatic involvement
Toxicity	Mild abdominal pain and nausea in 12% of the patients. Mild cholecystitis: 10%. 7% grade 2 and 3 gastritis. Two hepatic failures in patients with >50% liver involvement
Conclusions	The combined treatment of TACE and systemic chemotherapy may prolong survival for liver metastases in breast cancer after mastectomy

6.4.5 Recommendation

Breast carcinoma is rarely a disease with liver-limited metastases. However, liver metastases of breast carcinoma have a very poor prognosis. Considering this problem, it has been tried to use locoregional treatment in these cases. TACE seems to be active and could be proposed to very selected patient; experience of HAI is very scarce and no conclusion can be given.

6.5 Liver Metastases of Kidney Cancer

Nabil et al. (2008) [40]

Concept	TACE of liver metastases
N	22
Inclusion criteria	Liver metastases after resection of primary tumor
Therapy	TACE: 10 mg/m^2 mitomycin C alone (45%) or in combination with 1000–2000 mg gemcitabine + Lipiodol + 200–450 mg DSM Every 4 weeks (mean 6 cycles)

Response rates	RR (%): 14 PR, 14%; SD, 59%; PD, 27%
Survival	Median survival: 7 months (from start of TACE) no statistical difference between therapy concepts (MMC vs. MMC + gemcitabine)
Toxicity	Postembolization syndrome (nausea, vomiting, or right upper quadrant pain) ($N = 10$), puncture site hematoma ($N = 1$), no major complications
Conclusions	TACE can result in a favorable local tumor response in patients with hepatic metastases from RCC, but survival results are still limited

Abdelmaksoud et al. (2012) [41]

Concept	Radioembolization with ^{90}Y
N	6
Inclusion criteria	Chemorefractory liver-dominant metastases from RCC
Therapy	Bi-lobar treatment with 120 Gy (infusion of ^{90}Y microspheres)
Response rates	Time to partial response: 133 days CR, $N = 3$; PR, $N = 1$; PD, $N = 2$
Survival	Median survival: 300 days
Toxicity	Grade 1 + 2 toxicities in all patients (primarily fatigue)
Conclusions	^{90}Y hepatic treatment could be an option for patients with liver-dominant metastatic RCC, intolerant to targeted therapies

6.5.1 Recommendations

The number of patients with liver-limited disease of kidney cancer and treated with intra-arterial hepatic chemotherapy is very limited, and there is no possibility to propose any recommendation, even if some data are encouraging.

The conclusion of this chapter is quite similar to the conclusion of a recent overview of intra-arterial treatment on non-colorectal liver metastases [42]: Despite many years of clinical use and documented efficacy on intra-arterial treatments of the

liver, there are still only a few prospective multicenter trials with many different protocols. Further large randomized trials and transparent guidelines need to be established.

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