• Review Article •

Regional chemotherapy for uveal melanoma liver metastases

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Abstract

● Chemotherapy remains an important approach for the treatment of liver metastases from uveal melanoma (UM). Compared with systemic chemotherapy, regional chemotherapy has similar efficacy and fewer systemic adverse effects. Regional chemotherapy for UM liver metastases includes hepatic artery infusion (HAI), transarterial chemoembolization (TACE), and isolated hepatic perfusion (IHP). In this review, we aim to examine the efficacy of regional chemotherapy and compare HAI, TACE, and IHP in terms of overall survival (OS). The three approaches showed no obvious difference in OS results.

● **KEYWORDS:** uveal melanoma; liver metastasis; regional chemotherapy

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INTRODUCTION

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults[1]. About 50% of UM patients will develop metastases with a survival of 4-15mo from the onset of metastasis[2]. Liver is the most common site of metastasis. There have been considerable advances in recent years with regard to the management of hepatic metastasis in UM, including immunotherapy and targeted therapy, but with modest results similar to systemic chemotherapy[3-5]. Tebentafusp, a novel form of immunotherapy, has shown promising results but is only indicated in patients who are positive for HLA-A*02:01[6-8]. It is not widely used currently and is not available outside the United States, Europe, and a few countries[9]. Thus, chemotherapy remains an important approach for the treatment of liver metastases from UM.

Regional chemotherapy for UM liver metastases includes hepatic artery infusion (HAI), transarterial chemoembolization (TACE), and isolated hepatic perfusion (IHP). Compared with systemic chemotherapy, regional chemotherapy has similar efficacy and fewer systemic adverse effects[10]. Regional chemotherapy is an ideal therapeutic option for metastasis confined exclusively to the liver. In this review, we aim to examine the efficacy of regional chemotherapy and compare HAI, TACE, and IHP in terms of overall survival (OS).

Hepatic Arterial Infusion HAI uses a surgically implanted pump or an arterial catheter connected to an external pump to deliver chemotherapy agents directly into the liver[11-12]. It is indicated for liver metastasis not amendable to complete surgical resection. The contraindications to HAI are liver involvement >70% or bilirubin >2-3 mg/dL. The common complications of HAI include gastrointestinal symptoms, chemical hepatitis, and bone marrow toxicity.

We searched PubMed with the search terms “hepatic artery infusion”, “intra-arterial chemotherapy”, “uveal melanoma”, and “ocular melanoma”. Ten studies investigated the efficacy of HAI in UM liver metastases (Table 1)[13-22]. There were six retrospective studies, three prospective studies, and one randomized trial. In total, 439 patients treated with HAI were described, ranging from 7 to 171 per study. The median OS ranged from 2.9 to 22mo. Fotemustine was the most commonly used drug. Other chemotherapeutic agents included carboplatin, cisplatin, vinblastine, dacarbazine, mitomycin, doxorubicin, and gemcitabine. Using carboplatin, Cantore *et al*[13] reported an overall response rate (ORR) of 38% and a median OS of

Table 1 Studies of HAI in UM patients with liver metastases

Study	Year	Study design	Intervention	Patients enrolled	ORR	DCR	Tumor response criteria	mPFS	mOS
Cantore[13]	1994	Prospective phase II study	Carboplatin	8	38%	50%	WHO	NR	15mo
Leyvraz[14]	1997	Prospective phase II trial	Fotemustine	31	40%	NR	WHO	NR	14mo (after diagnosis)
Egerer[15]	2001	Prospective pilot study	Fotemustine	7	28.6%	71.4%	WHO	NR	18mo
Peters[16]	2006	Retrospective	Fotemustine	101	36%	84.2%	WHO	NR	15mo
Siegel[17]	2007	Retrospective	Fotemustine	18	27.8%	61.1%	WHO	NR	22mo
Melichar[18]	2009	Retrospective	Cisplatin + vinblastine + dacarbazine	10	20%	60%	WHO	NR	16mo
Farolfi[19]	2011	Retrospective case series	Fotemustine/carboplatin	18	16.7%	38.9%	RECIST 1.1	6.2mo	21mo
Heusner[20]	2011	Retrospective	Melphalan or melphalan followed by other chemoperfusion agents	61	8%	56.7%	RECIST	NR	10mo
Leyvraz[21]	2014	Multicentric randomized trial	Fotemustine	171	10.5%	NR	RECIST 1.0	4.5mo	14.6mo
Boone[22]	2018	Retrospective	Melphalan	14	7%	28%	NR	NR	2.9mo

HAI: Hepatic artery infusion; UM: Uveal melanoma. ORR: Overall response rate; DCR: Disease control rate; mPFS: Median progression-free survival; mOS: Median overall survival; NR: Not reported; WHO: World Health Organization; RECIST: Response Evaluation Criteria in Solid Tumors.

15mo with minor liver-related toxic effects. Leyvraz *et al*[14] conducted a prospective phase II trial with fotemustine, which showed the highest ORR of 40%. The study of Peters *et al*[16], also using fotemustine, reported the highest disease control rate (DCR) of 84.2%. The longest median OS was observed in the study by Siegel *et al*[17], reaching up to 22mo. On the other hand, the study by Boone *et al*[22] showed a median OS of 2.9mo with melphalan. The reported ORR and DCR were also lower than other studies, because the patients enrolled in this study had extremely advanced disease and were near the brink of liver failure. In the retrospective case series by Farolfi *et al*[19], no differences were found in toxicity or clinical outcome between fotemustine and carboplatin. Small sample size (n=18) might be the possible reason. The only randomized trial was conducted by Leyvraz *et al*[21], comparing hepatic intra-arterial and intravenous fotemustine. They found no difference in OS, but intra-arterial showed better ORR and progression free survival (PFS).

Transarterial Chemoembolization TACE combines intra-arterial chemotherapy with embolization of arterial supply to the tumor. The chemotherapeutic agents are directly delivered to the tumor in the liver through a catheter inserted into the femoral artery in the groin. The embolization can be accomplished using polyvinyl/gelatin sponges, polyvinyl alcohol particles, microspheres, and drug-eluting beads[23]. This technique entraps a high concentration of chemotherapy to the tumor and also cuts off the tumor's oxygen and nutrient supply[24]. Compared with other embolization approaches, drug-eluting beads can deliver stable therapy over time, achieving a higher DCR[25-28]. The contraindications to TACE are liver involvement >70%, main portal vein thrombosis, Child-Pugh C, and arterio-portal fistula. The common complications of TACE include decompensation with edema/ascites, acute cholecystitis, acute pancreatitis, liver rupture, liver abscess, renal failure, and postembolization syndrome[29]. We searched PubMed with the search terms "transarterial chemoembolization", "chemoembolization", "uveal melanoma", and "ocular melanoma". Nineteen studies investigated the efficacy of TACE in UM liver metastases (Table 2)[30-48]. There were thirteen retrospective studies, five prospective studies, and one randomized trial. In total, 733 patients treated with TACE were described, ranging from 5 to 201 per study. The median OS ranged from 5.2mo to 23mo. Cisplatin was the most commonly used drug. Other chemotherapeutic agents included vinblastine, dacarbazine, vincristine, dactinomycin, carmustine, mitomycin C, doxorubicin, irinotecan, paclitaxel, carboplatin, and melphalan. Though fotemustine and carmustine have pharmacological advantages for local intra-arterial treatment of liver metastases, no comparative clinical trial has shown that they have better results than cisplatin or other agents. Mavligit *et al*[30] used cisplatin and polyvinyl sponge, achieving an ORR of 46% and a median OS after metastases diagnosis of 11mo. Bedikian *et al*[31] retrospectively reviewed 201 cases and compared the results of systemic therapies, hepatic intra-arterial chemotherapies, and chemoembolization. The study showed that chemoembolization was the most effective treatment, with an ORR of 36%. Agarwala *et al*[32] conducted a randomized phase I/II trial evaluating intrahepatic chemotherapy with cisplatin with or without polyvinyl sponges. They reported an ORR of 16% and a median OS of 8.5mo. Besides, the results of this study indicate that the maximum tolerated dose of cisplatin for direct hepatic artery infusion is 125 mg/m^2, given with or without embolization. At 125 mg/m^2, half of the patients experienced grade 3 or higher toxicity (renal, hematological, and hepatic toxicity). Using carmustine, Patel *et al*[33] and Gonsalves *et al*[45] reported a median OS of 5.2mo and 7.1mo. There were four studies using irinotecan-charged beads:

Table 2 Studies of TACE in UM patients with liver metastases

Study	Year	Study design	Intervention	Patients enrolled	ORR	DCR	Tumor response criteria	mPFS	mOS
Mavligit[30]	1988	Retrospective	Cisplatin + polyvinyl sponge	30	46%	NR	WHO	NR	11mo (after diagnosis)
Bedikian[31]	1995	Retrospective	Cisplatin + polyvinyl sponge/ cisplatin + vinblastine + polyvinyl sponge/ cisplatin + dacarbazine + vincristine + polyvinyl sponge/cisplatin + dacarbazine + polyvinyl sponge/ cisplatin + dactinomycin + polyvinyl sponge	201	36%	50%	WHO	NR	6mo
Agarwala[32]	2004	Prospective randomized phase I/II trial	Cisplatin with or without polyvinyl sponge	19	16%	84%	WHO	NR	8.5mo
Patel[33]	2005	Prospective phase II trial	Carmustine + gelatin sponge	30	20.8%	75%	RECIST	NR	5.2mo
Vogl[34]	2007	Prospective pilot study	Mitomycin C + microspheres	12	NR	NR	WHO	NR	21mo
Dayani[36]	2009	Retrospective case series	Cisplatin + doxorubicin hydrochloride + mitomycin + gelatin sponge/polyvinyl alcohol particles	21	NR	NR	RECIST	NR	7.6mo
Fiorentini[35]	2009	Prospective phase II trial	Irinotecan + drug-eluting beads consisted of polyvinyl alcohol microspheres	10	100%	100%	RECIST	NR	8 of 10 patients alive at 6.5mo midian follow-up time
Gupta[39]	2010	Retrospective	Cisplatin/cisplatin + paclitaxel/ cisplatin + doxorubicin + mitomycin + gelatin sponge/polyvinyl alcohol particles	125	11%	76%	WHO	3.8mo	6.7mo
Huppert[37]	2010	Prospective pilot trial	Cisplatin/carboplatin + polyvinyl alcohol particles	14	57%	86%	RECIST	8.5mo	11.5mo
Schuster[38]	2010	Retrospective	Fotemustine/cisplatin + starch microspheres	25	16%	72%	RECIST	3mo	6mo
Edelhauser[41]	2012	Retrospective, single-center	Fotemustine + polyvinyl alcohol particles	21	14%	43%	RECIST	7.3mo	28.7mo (after diagnosis)
Venturini[40]	2012	Prospective	Irinotecan + drug-eluting beads	5	60%	80%	RECIST	NR	All patients alive at 10.6mo midian follow-up time
Farshid[42]	2013	Retrospective	Mitomycin C + starch microspheres	20	25%	70%	RECIST 1.1	4.3mo	20mo
Duran[43]	2014	Retrospective, single-institution	Doxorubicin + mitomycin C + microspheres	15	0	40%/73%/60%	WHO/RECIST/ mRECIST	NR	5.6mo
Carling[44]	2015	Retrospective	Irinotecan + drug-eluting beads	14	0	15.40%	RECIST 1.1	NR	9.4mo
Gonsalves[45]	2015	Retrospective	Carmustine + gelatin sponge	50	6%	72%	RECIST 1.0	5.0mo	7.1mo
Valpione[46]	2015	Retrospective cohort study	Irinotecan charged microbeads	58	27.5%/94.1%	100%	RECIST 1.1/ mRECIST	NR	15.5mo
Shibayama[47]	2017	Retrospective	Cisplatin + gelatin sponge	29	21%	66%	RECIST 1.1	6mo	23mo
Carle[48]	2020	Retrospective, monocentric	Melphalan + microspheres	34	42.4%/97%	87.9%/97%	RECIST 1.1/ mRECIST	8mo	16.5mo

TACE: Transarterial chemoembolization; UM: Uveal melanoma; ORR: Overall response rate; DCR: Disease control rate; mPFS: Median progression-free survival; mOS: Median overall survival; NR: Not reported; WHO: World Health Organization; RECIST: Response Evaluation Criteria in Solid Tumors; mRECIST: Modified Response Evaluation Criteria in Solid Tumors.

Fiorentini *et al*[35] reported the highest ORR of 100%, never the less the study had a small sample size of 10 patients; Venturini *et al*[40], reported an ORR of 60% and a DCR of 80%; Valpione *et al*[46] reported a median OS of 15.5mo; However, the study of Carling *et al*[44] showed that the effect of drug-eluting beads loaded with irinotecan alone on OS is questionable; Longest median OS was observed in the study by Shibayama *et al*[47], reaching up to 23mo. Carle *et al*[48] reported a median OS of 16.5mo with melphalan.

Isolated Hepatic Perfusion IHP involves temporary vascular isolation of the liver and perfusion of high-dose chemotherapeutic agents while limiting extrahepatic toxicity[49]. It is used mainly for patients with surgically unresectable liver tumors. Percutaneous Isolated Hepatic Perfusion (PHP) is a minimally invasive alternative to IHP and is repeatable[50]. IHP/PHP is indicated for tumors totally or predominantly localized to the liver. The relative contraindications to IHP/PHP include insufficient liver function (bilirubin >1.5 mg/dL, elevated INR, platelet <100 000), portal hypertension, intolerance to heparin, and age >70[51]. The most common complication of IHP is bone marrow suppression. Complications related to vessel catheterization might occur as well.

We searched PubMed with the search terms “isolated hepatic perfusion”, “percutaneous hepatic perfusion”, “uveal melanoma”, and “ocular melanoma”. Twenty-eight studies investigated the efficacy of IHP and PHP in UM liver metastases (Table 3)[52-79]. There were seventeen retrospective studies and eleven prospective studies. In total, 814 patients treated with IHP or PHP were described, ranging from 3 to 101 per study. The median OS ranged from 4.5mo to 27.4mo. Melphalan was used in all studies. Hafström *et al*[52] used melphalan and cisplatin as chemotherapeutic agents, achieving a median OS of 4.5mo. Alexander *et al*[53] performed IHP using melphalan alone or with tumor necrosis factor (TNF), with a median OS of 11mo. The study reported a longer overall median duration of response in those treated with

Table 3 Studies of IHP/PHP in UM patients with liver metastases

Study	Year	Study design	Intervention	Patients enrolled	ORR	DCR	Tumor response criteria	mPFS	mOS
Hafström[52]	1994	Prospective phase I study	Melphalan + cisplatin	10	20%	50%	UICC	NR	4.5mo
Alexander[53]	2000	Prospective phase I/II study	Melphalan with or without TNF	22	54.5% (with TNF)/ 70% (without TNF)	14% (with TNF)/ 6% (without TNF)	WHO	NR	11mo
Alexander[54]	2004	Prospective phase I/II study	Melphalan	29	62%	NR	WHO	8mo	12.1mo
Noter[55]	2004	Prospective	Melphalan	8	50%	75%	WHO	6.7mo	9.9mo
Pingpank[56]	2005	Prospective phase I study	Melphalan	10	50%	NR	RECIST	NR	NR
van Iersel[57]	2008	Retrospective	Melphalan	13	33%	83%	RECIST	6.6mo	10mo
van Etten[58]	2009	Prospective	Melphalan	8	37.5%	75%	WHO	6mo	11mo
Varghese[59]	2010	Prospective	Melphalan	17	50%	NR	NR	NR	11.9mo
van Iersel[60]	2014	Prospective phase I study	Melphalan + oxaliplatin	3	33%	33%	RECIST	NR	18.7mo
Forster[61]	2014	Retrospective	Melphalan	5	80%	80%	RECIST	7.6mo (hepatic PFS)	14.2mo
Olofsson[62]	2014	Prospective phase II study	Melphalan	34	68%	85%	RECIST 1.1	7mo	24mo
Vogl[63]	2014	Prospective	Melphalan	8	37.5%	75%	RECIST	NR	NR
de Leede[64]	2016	Retrospective	Melphalan	31	NR	NR	WHO	6mo	10mo
Ben-Shabat[65]	2016	Retrospective	Melphalan/ Melphalan + cisplatin/ Melphalan + TNF	68	67%	87%	RECIST	10mo	22mo
Ben-Shabat[66]	2017	Retrospective	Melphalan with or without buffer	52	58% (with buffer)/ 88% (without buffer)	78% (with buffer)/ 100% (without buffer)	RECIST 1.1	9.2mo (with buffer)/ 17.6mo (without buffer)	24.2mo (with buffer)/ 26.0mo (without buffer)
Vogl[67]	2017	Retrospective	Melphalan	18	44.4%	83.3%	RECIST 1.1	12.4mo	9.6mo
Kirstein[69]	2017	Retrospective	Melphalan	11	33.3%	77.8%	RECIST 1.1	NR	NR
Karydis[68]	2018	Retrospective	Melphalan	51	49%	82%	RECIST 1.1	8.1mo	15.3mo
Artzner[70]	2019	Retrospective	Melphalan	16	60%	93%	RECIST 1.1	11.1mo	27.4mo
Brüning[71]	2020	Retrospective	Melphalan	19	53%	100%	RECIST 1.1	14.3mo	16.7mo
Schönfeld[72]	2020	Retrospective	Melphalan	30	42.3%	NR	RECIST 1.1	6mo	12mo
Meijer[73]	2021	Prospective phase II study	Melphalan	35	72%	85%	RECIST 1.1	7.6mo	19.1mo
Dewald[74]	2021	Retrospective, single-center	Melphalan	30	42.3%	80.8%	RECIST 1.1	6mo	12mo
Veelken[75]	2022	Retrospective	Melphalan	9	78%	NR	mRECIST	11.2mo (hepatic PFS)	13mo
Tong[76]	2022	Retrospective pooled analysis	Melphalan	101	59.4%	89.1%	RECIST 1.1	9mo	20mo
Modi[77]	2022	Retrospective	Melphalan	81	60.5%	88.9%	RECIST 1.1	8.4mo	14.9mo
Estler[78]	2022	Retrospective, single-center	Melphalan	29	37.9%	79.3%	RECIST 1.1	7.1mo	12.9mo
Dewald[79]	2021	Retrospective, two-center	Melphalan	66	59%	93.4%	RECIST 1.1	8.4mo	18.4mo

ORR: Overall response rate; DCR: Disease control rate; mPFS: Median progression-free survival; mOS: Median overall survival; NR: not reported; UICC: Union for International Cancer Control; WHO: World Health Organization; RECIST: Response Evaluation Criteria in Solid Tumors; mRECIST: Modified Response Evaluation Criteria in Solid Tumors; TNF: Tumor necrosis factor.

TNF than without TNF (14 versus 6mo; P=0.04). van Iersel *et al*[60] performed a phase I study to determine the optimal dose of oxaliplatin in combination with a fixed melphalan dose. They reported 100 mg as the maximal tolerated dose of oxaliplatin. However, the study indicated that applying this dose of oxaliplatin in IHP is not expected to improve results in patients with isolated hepatic metastases. Pingpank *et al*[56] performed PHP using melphalan and determined that 3 mg/kg is the maximum safe tolerated dose of melphalan administered *via* PHP. Ben-Shabat *et al*[66] retrospectively analyzed if adding a buffering agent to the perfusate during IHP would reduce toxicity and complication rates. The study showed that buffering would reduce the value of liver function tests, but could not reduce complication rates. In the study by Tong *et al*[76], positive predictors for survival in melphalan-PHP treated UM patients were identified, including primary tumor radiotherapy, normal baseline LDH, and PHP cycles.

DISCUSSION

The three regional chemotherapy approaches, HAI, TACE, and IHP, have their advantages and limitations. Compared with HAI, TACE has the benefit of trapping the chemotherapy in the tumor and also cutting off the supply of oxygen and nutrients to the tumor. Thus, TACE is more suitable for tumor with abundant blood supply. IHP is a more invasive treatment in comparison to HAI and TACE. Its alternative, PHP, is less invasive, but is still technically demanding[80-81].

The different growth patterns of hepatic metastases would result in different responses to regional chemotherapy. Hepatic metastatic UM has two radiographic growth patterns, namely nodular pattern and infiltrative pattern.

Compared with infiltrative pattern, nodular growth pattern on angiography indicates the tumor to be more responsive to chemoembolization or radioembolization.

The efficacy of different chemotherapeutic agents in the treatment of UM liver metastases is uncertain, and there is a lack of unified criteria. Further clinical trials excluding confounding factors are needed to identify more effective chemotherapeutic drugs. Our review shows that none of the chemotherapeutic drugs can significantly prolong the survival time of patients, which merits more basic experiments looking for UM-sensitive drugs.

The three approaches showed no obvious difference in OS results. There exist variations in the survival data within each approach, which may be due to different inclusion criteria of different studies. The burden of liver tumor, previous treatment, and extrahepatic metastasis may hinder the fair comparison of survival data. Further randomized controlled trials are required to evaluate the efficacy of the three methods.

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