Transcatheter Chemo-Embolization for Hepatocellular Carcinoma and certain Hepatic Metastasis

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Introduction

Hepatocellular Carcinoma (HCC) is extremely lethal and an overall median survival without treatment is 1.6 months.[1] There are two main causes of death: deterioration due to tumour growth, and hepatic failure. Prognostic factors include size and number of lesions, vascular invasion, infiltrative behavior, capsular invasion and distant metastasis. The prognosis is closely related to liver function reserves. Ohnishi et al[2] reported the natural history of HCC without treatment and demonstrated median survival times of 37 months for Child's A, 16 months for Child's B and 2 months for Child's C patients.

Okuda et al[1] introduced a simple and practical staging system for HCC. Only four clinical signs are used for the staging (a) more than 50% tumour size (b) ascites (c) less than 3mg/dl of serum albumin and (d) more than 3 mg/dl of serum bilirubin.

Stage I	-	no above signs
Stage II	-	1-2 clinical signs
Stage III	-	3-4 clinical signs

The median survival of 229 patients with no specific treatment at Stages I, II and III were 8.3 months, 2.0 months and 0.7 months respectively.

Detection of Early HCC

Establishment of screening ultrasound (US) and serum AFP of high risk groups such as hepatitis B or C carriers and liver cirrhotic patients and recent advances in medical imaging technology permit the early detection of small HCCs. The sensitivities of various imaging modalities for HCC of <3 cms is reported as:[3,4]

Ultrasound	46 - 84%
Helical CT	54 - 84%
Angiography	81%
CT arterioportography	88%
Iodized Oil CT	93%
MRI	90%
Intra-operative US	96%

Japanese recommendation for screening cirrhotic patients is to perform alpha-fetoprotein every 2 months, US every 3 months and CT or MRI every 6 months.[5]

Treatment of HCC

Hepatic resection offers the best chance at cure for patients with hepatocellular carcinoma, but only 10-30% of such patients are eligible for resection.[6] In addition, the recurrence rate in the remnant liver after a hepatectomy is markedly high, ranging from 36% - 66%.

The second best option would be hepatic transplantation, which is reserved for selected patients with cirrhotic liver disease who have tumour (diameter, <5 cm) in the context of neoadjuvant protocols. The long term survival is higher than resection[7,8] but treatment is restricted due to limited facilities, selection criteria and long wait for donor livers.

Unresectable HCCs pose a challenge to both oncologists and interventional radiologists. The results of systemic chemotherapy and radiotherapy have been disappointing with no appreciable impact on survival rates.[9] Although the direct application of intra-arterial chemotherapy into the feeding artery of a tumour is theoretically much more effective and produces less toxicity than systemic intravenous chemotherapy, the benefit and safety of this treatment has not been proved in clinical trials.[10,11]

Hepatic artery embolization, in combination with chemotherapy was developed in Japan in early 80s for unresectable HCC.[12] It is now fairly well established as primary treatment for non-resectable HCC.[13] The rationale for transarterial chemo-embolization (TACE) is that these tumours especially the well-encapsulated lesions are mainly fed by the hepatic artery. By contrast the infiltrative tumours also have a supply from the portal vein. On the basis of many clinical studies[14] it has been speculated that when iodized oil (Lipoidol Ultra-Fluid) is used to embolize HCC, the oil enters the sinusoids, where it is retained. Oil particles have been found in the portal vein following an arterial injection. The oil is mixed with the cytotoxic agent such as Cisplatinum, Doxorubicin, Epirubicin or Mitomycin C to form a covalent conjugate, which is then injected into the feeding artery. The conjugate remains in the tumour acting from both arterial and portal side and the cytotoxic agent is slowly released to exert the chemotherapeutic effect. Lipoidol serves as both the targeting agent that carries the cytotoxic agent to the tumour, since it is selectively deposited in it and the embolizing agent that causes

blockade of neovasculature of the tumour. The daughter tumours are also dealt with in the segment or lobe which is injected.[15]

Gelfoam particles appear to be essential to maximize the therapeutic effect of TACE. They increase the retention of iodized oil by blocking washout. Takuyasu et al[16] found that complete necrosis occurred in 83% with triple therapy (Lipoidol, adriamycin and gelfoam), but occurred in only 13% with oil and adriamycin.

Results of TACE

Several reports from the 1990's consistently show a 2-3 fold increase in median survival after chemoembolization compared to untreated controls[17,18] (Table). Survival varies directly with tumour encapsulation, oil uptake and retention, and inversely with tumour volume, infiltration and underlying liver disease. Post-operative recurrent HCCs have also been treated by TACE.[19] Iodized oil can reach recurrent tumours even through the small collateral vessels that often develop after repeated TACE and previous surgery. Although unresectable tumours have become resectable after successful TACE[20], pre-operative TACE for resectable HCCs is controversial.

Choice of Chemo Agent

Doxorubicin Hydrochloride (Adriamycin [ADR]) has been the main anticancer agent used in TACE. The standard dose is 20-30 mg/m^2 (20-90 mg; mean 40 mg). The dose would be adjusted according to the size and number of tumours, embolized area and liver function.

Table. Western Series of TACE for Hepatocellular Carcinoma.

Autho	Year	Therapy	No.	Median Survival Months	P
Prospective, randomized					
Pelletier[30]	1990	Dox + Gel	21	4	NS
		Supportive Care	21	6	
French group[31]	1995	Cis + Lip + Gel	50	19	0.13
		Supportive Care	46	8	
Retrospective, matched historical Controls					
Vetter[32]	1991	Dox + Lip + Gel	30	12	<0.001
		Supportive Care	30	3	
Bronowicki[33]	1994	Dox.Cis, or Epi+Lip+Gel	127	18	<0.0001
		Supportive Care	127	5	
Stefanini [34]	1995	Dox + Lip + Gel	69	21	<0.001
		Supportive Care	64	3	
Retrospective, nonmatched controls					
Bronowicki [35]	1996	Dox,Cis,or Epi+Lip+Gel	42	36	<0.0001
		Supportive Care	33	11	
Stuart [36]	1996	Dox + Lip + Gel	137	14	<0.01
		Supportive Care	81	2	
Marcos-Alvarez[37]	1996	Dox + Lip + Gel	30	13	<0.05
		Supportive Care	22	5	
Ryder[38]	1996	Dox + Lip + Gel	67	9	NA
		Non-Surgical Therapy		118	3
Rose[18]	1998	Dox + Lip + Gel	35	9	<0.0001
		Supportive Care	31	3	

Dox = doxirubicin; Cis = cisplatin; Epi = epirubicin; Lip = lipiodol; Gel = gelatin-foam particles or powder; NS = not statistically significant; NA = not applicable.

Epirubicin (EPI), analog to Adriamycin, has less acute toxicity (nausea, vomiting), less myelosuppression on an equivalent milligram basis and higher total allowed cumulative dose before the onset of congestive heart failure.[21] To attain equivalent biological effect of ADR, approximately 25% more EPI must be given, so that 25-40 mg/m2 is equivalent to 20-30 mg/m^2 of ADR.

Cisplatinum (60 mg/m^2) and Mitomycin C (0.2 mg/Kg) are effective alternatives. They can be used when a patient shows clinical evidence of ADR cardiotoxicity or when a synergestic effect is anticipated.

Complications

Overall complication rate of TACE is reported to be 4.4%[22] and related to the use of chemoembolic agents or the manipulation of a catheter or guide wire. The most common complication is post embolization syndrome (nausea, vomiting, abdominal pain, loss of appetite and daily intermittent fevers - temperature below 39°C). This syndrome can occur with any solid organ embolization. With current medical care (hydration, antiemetics and pain control) the symptoms are well tolerated and 50% of patients can be discharged from the hospital the day following chemoembolization. Extent and duration of fever appears to be related to the degree of tumour necrosis and to tumour size. These symptoms improve with time.

Other complications are listed below[23]:

1.	Puncture site hematoma	1.6%
2.	Peripheral artery occlusion	0.4%
3.	Catheter induced complications	0.4%
4.	Contrast media reactions	4.0%
5.	Renal failure	2.4%
6.	Prolonged fever	0.4%
7.	Liver abscess	0.4%
8.	Mortality	2.0%
9.	Liver infarction	0.17%
10.	Acute hepatic failure	0.26%
11.	Intrahepatic biloma formation	0.87%
12.	Cholecystitis and gallbladder infarction	0.30%
13.	Splenic infarction	0.08%
14.	GI mucosal lesions	0.22%
15.	Tumour rupture	0.04%
16.	Variceal bleeding	0.13%

Toxicity

Mild to moderate elevation of AST or LDH are frequently noted that peaks at 3-5 days after TACE but hepatic function usually recovers within a few weeks.[24] Recovery of hepatic function is delayed in patients with markedly decreased hepatic reserve. There is no sustained degradation of liver function in properly selected patients who do not meet the well-established exclusion criteria for TACE, even in the presence of cirrhosis .[25] Because most of the injected drug is retained in the liver, systemic toxicity is minimized, with little bone marrow suppression. The cumulative toxicity is far more limited than is experienced with systemic chemotherapy.

Factors, which can minimize hepatotoxicity are:

1. Child A and Child B cirrhosis
2. Patent portal vein
3. Hepatopetal flow in portal vein
4. Superselective catheterization of tumour feeders
5. Use of gelfoam pledgets (>500um) rather than gelfoam powder
6. Dose calculated according to the size of tumour and liver function reserve

TACE for Treatment of Liver Metastasis

Colorectal Metastasis

Phase II studies of chemoembolization for metastasic colorectal cancers have been reported by several centers in US with promising results. At the Boston Center for liver cancer, 40 paients were chemoembolized[26] with 5FU, Mitomycin C, oil and gelfoam. Sixty three percent had partial or minor morphological responses and 62% had a 50% drop in CEA level. Median survival from first chemoembolization was 10 months. At the University of Pennysylvania, 51 patients were chemoembolized.[27] Morphological stabilization or regression occurred in 72%, CEA stabilized or regressed in 90% and the median duration of response was 12 months. The ACR Imaging Network is currently funding a multicenter Phase III randomized trial of systemic chemotherapy with or without chemoembolization for colorectal metastasis to liver.

Ocular Melanoma

Patients with ocular melanoma frequently develop rapidly progressive fatal hepatic metastasis, with median survival of 2-6 months. The M. D. Anderson Cancer Center reported on 30 patients treated by chemoembolization.[28] There was one complete response and 46% of the patients had a >50% morphological response. Median survival was 11 months.

Neuroendocrine Tumours

Embolization has an established role in the palliation of these hypervascular tumours, typically producing symptom-free intervals of 5-10 months in 90-100% of patients.[29] Other investigators have warned of an increased

complication rate for chemoembolization of carcinoid tumours.

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