Therapy for unresectable hepatocellular carcinoma: review of the randomized clinical trials—I: hepatic arterial embolization and embolization-based therapies in unresectable hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is common worldwide and frequently fatal. Despite the availability of potentially curative therapies for localized HCC, most patients have unresectable tumor, either at presentation or recurrence. We reviewed 18 randomized trials investigating hepatic arterial embolization-based therapies. Therapy for unresectable HCC is difficult, both because of advanced stage at presentation and accompanying liver dysfunction. Clinical investigations in HCC have been impaired by heterogeneity of enrolled subjects, limited sample sizes and uncertainties regarding optimal mechanisms of delivering therapy. Despite initial reports which suggested limited benefit to hepatic artery embolization-based treatment, more recently published, well-conducted studies demonstrate a survival benefit conferred by hepatic artery chemoembolization. Chemoembolization likely confers a benefit greater than that associated with embolization without chemical agents. There is limited evidence and consensus regarding optimal choice and dosage of chemical agents utilized for hepatic artery chemoembolization. *Anti-Cancer Drugs* 15:427–437

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common neoplasms worldwide. Estimates of global incidence and mortality per year range between 400 000 and 1 million cases. The highest HCC incidence occurs in Sub-Saharan Africa and Southeast Asia (the incidence in Taiwan is 150 cases per 100 000 population per annum). Intermediate incidence regions include Eastern and Southern Europe, the Middle East, and South America [1–3]. Although HCC occurs less frequently in Northern Europe and the US, incidence in the US has increased dramatically in recent years, largely because of the prevalence of chronic hepatitis C (HCV) infection (estimated at nearly 4 million cases in the US) [4]. HCC occurs most frequently in patients with cirrhosis commonly due to chronic infection with HBV and HCV and longstanding alcohol abuse [1,5]. Less common causes include autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and aflatoxin exposure.

Curative therapy for HCC is feasible for patients presenting with limited disease (unilobar tumors with absence of major vascular invasion or metastasis); these treatments include surgical resection, liver transplantation, alcohol injection and radiofrequency ablation. However, only 10–30% of patients diagnosed with HCC are eligible for such therapies, predominantly because of advanced tumor at presentation. HCC recurrence is common following surgical resection (and other potentially curative treatment), with 5-year survival following surgery as low as 30% in some series [6,7]. Hence, the overwhelming majority of HCC patients are candidates for medical therapy at some point during the course of disease [8].

Purpose of review

There exists limited consensus regarding therapeutic standards-of-care in unresectable HCC. Hepatic artery embolization is frequently undertaken at centers with experience in HCC treatment. However, many HCC patients are not candidates for embolization-based therapy (because of limited hepatic function, advanced hepatic tumor or metastatic disease). Although many HCC clinical trials have not demonstrated therapy to be efficacious, some of the more recently published investigations suggest that treatment may confer survival and quality-of-life benefit [9]. Because of the absence of consensus regarding management of unresectable HCC, because of interesting results reported since the publication of prior comprehensive reviews and because many randomized studies could not be included in recent

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meta-analyses, we reviewed randomized trials in unresectable HCC [10–12].

Methods

A Medline search was performed through December 2002 using the MeSH term *liver neoplasms*, and limiting the results to randomized controlled trials and publications in English. The Pubmed search terminology was: ((“*liver neoplasms*” [MeSH Terms] AND *Randomized Controlled Trials* [ptyp]) AND *English* [Lang]). The MeSH term *carcinoma, hepatocellular* was not used because it is subordinate to liver neoplasms and its inclusion in the search strategy did not change the result. The Medline search identified 405 articles. Earlier review papers and textbook chapters were also evaluated [10,13].

Medline search results were reviewed independently by two co-authors (discrepancies were resolved by consensus). Articles were excluded from subsequent review if they did not address HCC (e.g. metastases from colon cancer), did not test a therapeutic intervention (e.g. prevention of HCC), were limited to supportive care (i.e. no anticancer treatment, e.g. management of esophageal varices), did not include prospectively randomized data or included preliminary data without reporting on therapeutic impact upon survival. If the information from Medline (i.e. titles, abstracts, keywords, etc.) did not permit exclusion, the full publication was reviewed in a subsequent step. Articles were further divided into three groups as follows: (i) neo-adjuvant and adjuvant trials in surgically resectable HCC (this was the subject of our recent review) [14], (ii) hepatic arterial embolization and embolization-based therapies in unresectable HCC (Part I of this report), and (iii) systemic and local non-embolization-based therapies in unresectable HCC (Part II of this report).

Results

In total, 406 Medline citations were identified via the search strategy described above. Of these citations, 279 were readily identified as pertaining to subjects not within the purview of this paper (i.e. involving diseases other than HCC, not investigating anti-HCC therapy, not randomized, etc.). Of the remaining 127 papers, 21 concerned adjuvant therapy (13 of which met criteria and were included in our 2002 review). Articles were excluded from this report as follows: 19 contained preliminary data only (no significant information regarding survival), nine were not randomized, nine involved patients with surgically resectable disease, one involved supportive-care interventions only, one involved commentary on previously published data and five involved diseases other than HCC.

Eighteen articles investigating hepatic artery embolization-based therapy met criteria for review. Of these randomized trials, 12 were from Asian centers (People’s Republic of China $n = 5$, Japan $n = 4$, Hong Kong $n = 2$, Taiwan $n = 1$) and six studies were from Europe (France $n = 3$, Spain $n = 2$, Greece $n = 1$). A significant survival benefit was reported in 33% (six of 18), and an additional two studies reported results and survival benefit in patient subsets only. Four studies randomized over 200 patients, two involved 100–200 subjects, nine involved 50–100 subjects and three trials randomized fewer than 50 patients. In seven of the 18 trials, sample size was based on statistical power. Side-effects were graded in one study; 11 studies provided detailed description and five studies provided limited discussion of side-effects.

Chemoembolization versus supportive care or non-beneficial systemic therapy

Seven studies involving 546 patients compared chemoembolization to supportive care or systemic therapy not currently associated with clinical benefit (two trials). The number of embolizations varied (the mean number of treatments ranged from 1 to 4.5 in the different trials). Enrollment occurred between 1984 and 2000. Five of the studies were European (France and Spain) and two were Asian (Taiwan and Hong Kong). The majority of European subjects had either HCV or alcohol-related cirrhosis. Asian patients were predominantly infected with HBV. The more-recently published studies have tended to include healthier subjects (Child–Pugh class A or B liver dysfunction) and those with more limited tumor extent. Four trials enrolled subjects from a single center; three were multicenter (see Table 1).

Specific studies

During the 1980s, Lin *et al.* conducted a three-arm trial of hepatic arterial embolization (TAE) involving 63 Taiwanese patients [15]. Eighty percent of patients were HBV-infected; the extent of liver dysfunction was not stated. One arm involved monthly TAE (mean of 2.1 treatments per patient). A second group received a single TAE followed by monthly high-dose 5-flourouracil (5-FU; $1\,g/m^2 \times 5$ days, with a mean of 3.1 treatments per patient). A third arm received monthly 5-FU only (mean of 2.8 treatments per patient). One-year survival for the group receiving ongoing TAE was superior to those receiving TAE/5-FU or 5-FU only [42, 21 and 13% respectively; the difference between the ongoing-TAE arm and the 5-FU-only arm was considered statistically significant ($p < 0.01$)]. Two-year survival was 25, 21 and 13%, respectively; these differences did not achieve significance. Three patients suffered major, non-fatal embolization-related complications (cholecystitis and gastric ulcer). There was no hepatic failure or abscess formation in any patient following TAE. Pain and fever occurred in over 50% of patients.

Table 1 Trials comparing chemoembolization versus supportive care or non-beneficial systemic therapy

Publication	Intervention	Mean no. of sessions	Survival				Liver disease	Tumor extent	Comment/misc.
			Medn	1-year	2-year	Sign			
Lin *Gastroenterology* 1988	TAE: $n=21$ TAE + i.v. 5-FU (1 g/m^2 × 5d) q month: $n=21$ i.v. 5-FU (1 g/m^2) q month: $n=21$	2.1 3.1 2.8		42%* 21% 13%*	25% 21% 13%	*$p<0.01$	80% HBV	Not stated	OS differences were reported as significant at 1 year, not at 2 years
Pelletier *J Hepatol* 1990	TACE (doxorubicin 50 mg): $n=21$ No anticancer therapy: $n=21$	2	~4 m ~6.5 m	24% 31%		NS	70% etoh 52% Okuda 2 22% Okuda 3 50% ascites	Median tumor: 34–41% of liver volume	
Group d' Etude et de Traitment du Carcinome Hepatocellulaire *N Eng J Med* 1995	TACE (cisplatin 70 mg + lipiodol): $n=47$ No anticancer therapy: $n=45$	2.9		62% 43%	38% 26%	NS	78% etoh 100% Child's A 90% Okuda I	41% multifocal 13% diffuse 7% portal branch inv.	Liver failure developed in 60% of TACE group
Bruix *Hepatology* 1998	TAE ± steel coil: $n=40$ No anticancer therapy: $n=40$	1.4		70% 72%	49% 50%	NS	62% HCV 82% Child's A 68% Okuda I 23% Okuda II	76% multifocal or massive	27% 4-year survival in control group
Pelletier *J Hepatol* 1998	TACE (cisplatin 2 mg/kg + lipiodol) + tamoxifen 40 mg p.o. qd: $n=37$ Tamoxifen 40 mg p.o. qd: $n=36$	2.8		51% 55%	24% 26%	NS	15% HBV 16% HCV 53% etoh 77% Child's A 23% Child's B 60% Okuda I 29% Okuda II	Not stated	Liver failure developed in 51% of TACE group
Lo *Hepatology* 2002	TACE (cisplatin max. 30 mg + lipiodol): $n=40$ No anticancer therapy: $n=39$	4.8		57% 32%	31% 11%	$p=0.002$	80% HBV 47% Okuda I 53% Okuda II	41% solitary 50% multifocal Median: 7 cm 26% portal branch inv.	
Llovet *Lancet* 2002	TAE: $n=37$ TACE (lipiodol + doxorubicin 25–75 mg/m^2): $n=40$ No anticancer therapy: $n=35$	3.1 2.8		75% 82% 63%	50% 63% 27%	$p=0.025$	85% HCV 70% Child's A 65% Okuda I 35% Okuda II	27% solitary 73% multifocal Median: 4.4–5.2 cm	

HCV = hepatitis C virus; HBV = hepatitis B virus; TAE = transarterial embolization; TACE = transarterial chemoembolization; 5-FU = 5-fluorouracil; tx = treatment; ~ indicates approximate value extrapolated from Kaplan–Meier curve (actual statistic not reported); NS = non-significant difference; inv. = invasion; m = month.

In 1990, Pelletier *et al.* reported results of a multi-institutional study [16]. Forty-two patients (predominantly with alcohol-induced liver disease) were randomized to receive either chemoembolization (including doxorubicin) or conservative management. Chemoembolization was repeated 2, 6 and 12 months following the initial treatment. The mean number of treatments per patient was 2. Fifty percent of the patients had evidence of liver decompensation (ascites) upon entry and had tumor involving over one-third of total liver volume. Although an objective tumor response was seen in 33% of patients in the TACE group, there was no difference in survival (24 and 31% at 1 year, respectively). Chemoembolization-related side-effects included hepatitis, acute renal failure and gastrointestinal hemorrhage. Pain and fever were also common.

Between 1990 and 1992, the French Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire conducted a randomized trial involving 24 institutions comparing TACE to conservative management [17]. Chemoembolization included cisplatin and lipiodol, and was repeated at 2-month intervals (mean of 2.9 treatments). Although many patients had well-compensated liver function (100% Child–Pugh Class A liver function; 90% Okuda Stage I), 13% of subjects had diffuse tumor and nearly one-half had multifocal disease. Patients assigned to the control group had a higher rate of portal vein thrombosis (PVT) than the TACE group (13 versus 2%, respectively) and a higher tumor burden (greater than 50% liver volume) than the TACE group (15 versus 6%, respectively). The trial was stopped after a scheduled analysis failed to demonstrate a 50% increase in survival at 8 months. There was a trend towards decreased death (RR 1.4, CI 0.9–2.2) in the chemoembolization arm. Hospitalization was more frequent in the TACE group. Sixty percent of the 50 patients who underwent chemoembolization developed liver failure, defined as encephalopathy, ascites or bilirubin elevation. Eighty-six percent of the chemoembolization patients developed abdominal pain, fever or vomiting.

The lack of survival benefit despite significant tumor response led investigators to modify approaches in subsequent trials; these included more restrictions on tumor extent and liver dysfunction, and continued variations concerning use of chemotherapeutic agents (including lipiodol), and frequency and intensity of embolization.

Bruix *et al.* conducted a randomized trial comparing embolization (without chemotherapy) versus symptomatic treatment [18]. Most of the 80 subjects had HCV-related liver disease and Child–Pugh Class A liver function. Forty patients received TAE with gelatin cubes; additionally, for those with unilobar HCC, a metal coil was placed to induce complete arterial occlusion. Most patients (60%) received a single embolization. Despite a 55% partial response rate, there was no difference in 2-year survival (50% for the treatment group, 49% for the control arm). The authors noted an unexpectedly high survival in the control arm (27% were alive at 4 years). Embolization was well tolerated and there was no difference in complications such as ascites, variceal bleeding, bacterial infection, encephalopathy or need for hospitalization. Performance status was similar in both groups at baseline and 2 years after treatment.

Pelletier *et al.* randomized 73 patients to receive ongoing TACE and oral tamoxifen versus tamoxifen alone [19]. Chemoembolization included cisplatin and lipiodol in addition to gelatin sponge particles; TACE was planned every 3 months during the first year and every 4 months subsequently. Patients underwent a median of three treatments. Most patients had alcohol-induced liver disease and Child–Pugh Class A liver function. Fever and abdominal pain were the most common side-effects of TACE. Liver decompensation occurred in 50% of the patients on the embolization arm. Embolization was associated with two fatalities (acute liver failure and gastric perforation). Side-effects of tamoxifen were not described. There was no difference in 1-year survival between the TACE and tamoxifen arms (51 and 55%, respectively).

Many of the studies discussed above were powered to demonstrate only large differences in survival and hence pooled analyses were attempted. However, authors providing review and meta-analyses of these studies arrived at disparate conclusions. In 1997, Simonetti *et al.* concluded that transcatheter arterial embolization provided a modest survival benefit [pooled odds ratio for 1-year survival of 2.0 (95% CI 1.2–4.6)] [10]. Trevisani *et al.* contended in 2001 that the anticancer effect of chemoembolization was outweighed by the deterioration of liver function [13]. Because reported endpoints were not uniform in many of the trials (i.e. 3-year survival is reported in one study, median survival in another), meta-analysis is not always feasible or can result in disparate conclusions.

Two more recent studies have demonstrated a survival benefit associated with TACE. Llovet *et al.* at the University of Barcelona randomized 112 predominantly HCV-infected patients to receive either chemoembolization, embolization or supportive therapy [20]. Selection criteria were such that only 12% of HCC patients evaluated for the study were enrolled. Seventy percent had Child–Pugh Class A liver function; 65% patients were classified Okuda Stage I and 35% as Okuda Stage II. Twenty-six percent of the tumors were solitary; 71% were multifocal and 4% were diffuse. The three treatment groups on this multicenter trial involved: chemoemboliza-

tion including doxorubicin and lipiodol (repeated at 2, 6 and every 6 months thereafter; mean number of treatments 2.8), embolization without chemotherapy via an identical schedule (gelfoam particles only; mean number of treatments 3.08), and symptomatic treatment. The trial was stopped early when a scheduled analysis indicated superior survival associated with chemoembolization. The 1-, 2- and 3-year survival rates for chemembolization were 82, 63 and 29%, compared to control-arm rates of 63, 27 and 17%, respectively ($p = 0.009$). Survival for those receiving embolization was 75, 50 and 29%, respectively. Chemoembolization was associated with reduced incidence of subsequent portal vein invasion (17 versus 58% at 2-year follow-up) and a risk-reduction in mortality of 0.47 (95% CI 0.25–0.91). Fewer than 10% of patients on the treatment arms had therapy discontinued because of therapy-related complications.

Lo *et al.* from the University of Hong Kong randomized 80 patients to receive chemoembolization including cisplatin and lipiodol versus symptom-oriented treatment [21]. Patients were predominantly HBV infected and had Okuda Stage I or II disease. Chemoembolization was repeated every 2–3 months (mean of 4.5 treatments per patient). Tumor response was noted in 39% of the treated patients. Survival in the chemoembolization group was 57, 31 and 26%, respectively, at 1, 2 and 3 years; survival in the control group was 32, 11 and 3%. The authors note that their control group's 2-year survival of 11% is comparable to that reported in other Asian series; this is lower than the 2-year survival reported for the control arm of the Barcelona group's study (27%). Although there has been significant speculation regarding intrinsic differences between HCC in European versus Asian populations, and between HCV- and HBV-infected patients, these potential differences have never been demonstrated conclusively in a prospective setting, and may be related to factors such as liver function and stage-at-presentation. It is worth noting that Lo's study included patients with invasion of portal vein branches (these patients were excluded from the Barcelona study) and that median tumor size was larger in this trial [7 cm (range of 4–14) versus 5 cm (range 3.9–6)] than in the Barcelona group's patients.

A recent meta-analysis incorporating data from the above seven trials also suggested a survival benefit conferred by hepatic arterial chemoembolization [9]. In this paper, Llovet and Bruix conclude that chemoembolization is associated with reduced risk of death at 2 years with an odds ratio ranging from 0.42 to 0.53, depending upon which trials are included in the assessment.

Conclusion

The more recently published trials provide more conclusive evidence that arterial embolization confers benefit in carefully selected patients with unresectable HCC. Chemoembolization (utilizing cisplatin and doxorubicin) may be more effective than embolization without antineoplastic agents. Patient selection is critical; the studies demonstrating robust benefit to therapy involved predominantly patients with well-preserved liver function and tumors which were neither diffuse nor involving extensive portions of liver volume. Advances in supportive care likely also have contributed to more successful outcomes with anticancer therapy in recent years. Optimal treatment schedule remains uncertain, although the studies by Llovet and Lo (mean number of treatments 2.9 and 4.8, respectively) suggest that ongoing therapy is often essential.

Hepatic artery chemoembolization utilizing different chemotherapy agents

Several groups have attempted to ascertain whether the addition of chemotherapy to embolization enhances survival. Five studies involving 1301 patients investigated different chemotherapeutic agents as components of hepatic chemoembolization. All five trials took place in Asia. Three were conducted in Tokyo or environs by the multi-institutional Cooperative Group for Liver Cancer in Japan (CGLCJ). Enrollment occurred between 1988 and 2000 (see Table 2).

Specific studies

In 1992, Kawai *et al.* reported on the Japanese Cooperative Group's initial data [22]. Their study evaluated the benefit of intra-arterial doxorubicin (40 mg/m^2) as a component of TAE. In total, 289 patients from 175 institutions with predominantly Child's A liver function were randomized to receive transcatheter arterial embolization (TAE) including lipiodol with or without doxorubicin (40 mg/m^2). Thirty-seven percent of patients received a second embolization and 19% had subsequent hepatic resection. The 1-, 2- and 3-year survival values for TAE with and without doxorubicin were 74.4, 51.3 and 33.6%, respectively, and 65.1, 42.4 and 34.9%, respectively. There was no significant difference. Anemia occurred more frequently in patients receiving doxorubicin (22.4 versus 9.6% in the control group).

A second study published by the same group compared hepatic chemoembolization with the addition of either farmorubicin (60 mg/m^2) or doxorubicin (40 mg/m^2) [23]. A total of 208 patients received farmorubicin and 207 patients received doxorubicin. There was no difference in tumor reduction rate, decrease in AFP or lipiodol accumulation. Survival at 6 months was not significantly different (82% doxorubicin versus 86% farmorubicin). There was a slight survival advantage associated with doxorubicin [1- and 2- year survival for doxorubicin was 74 and 57%, respectively, versus 69 and 44%, respectively, for farmorubicin ($p = 0.038$)]. Discussion of toxic effects

Table 2 Hepatic artery chemoembolization utilizing different chemotherapy agents

Publication	Intervention	Mean no. of sessions	Survival			Liver disease	Tumor extent	Comment/misc.
			1-year	2-year	Sign			
Kawai (CGLCJ) *Cancer Chemother Pharmacol* 1992	TACE (doxorubicin 40 mg/m^2): $n=141$ TAE: $n=148$		74% 65%	51% 42%	NS	76% Child's A 24% Child's B 63% Okuda I 31% Okuda II	72% solitary 17% multifocal or massive	
Kawai (CGLCJ) *Cancer Chemother Pharmacol* 1994 and *Semin Oncol* 1997	TACE (farmorubicin 72 mg/m^2): $n=208$ TACE (doxorubicin 40 mg/m^2): $n=208$		69% 74%	44% 57%	NS	70% Child's A 64% Okuda I 30% Okuda II	72% solitary 20% multifocal or massive	Analysis included 3-year survival (33 versus 37%)
Watanabe *Cancer Chemother Pharmacol* 1994	TACE (farmorubicin 60 mg/m^2): $n=39$ TACE (doxorubicin 40 mg/m^2): $n=38$	1 1	70% 75%	45% 44%	NS	56% Child's A 29% Child's B 32% Okuda I 47% Okuda II		
Chang *Cancer* 1994	TACE (cisplatin 50 mg/m^2): $n=22$ TAE: $n=24$	2.8 3	53% 73%	26% 40%	NS	65% Child's A	44% solitary 44% multifocal or massive 13% diffuse	
Chen *World J Gastroenterol* 2002	TACE (epirubicin 50 mg/m^2 + mitomycin 8 mg/m^2) + (lipiodol >20 cm^3): $n=216$ TACE (chemotherapy as above) + (lipiodol 5–15 cm^3): $n=257$		Child's A/B 79%/42% 59%/47%	Child's A/B 52%/21% 27%/24%	$p<0.001$	93% Child's A	29% PVT Tumor: 40%>15 cm 91%>10 cm	Survival reported only for Child's A and B groups separately

HCV = hepatitis C virus; HBV = hepatitis B virus; TAE = transarterial embolization; TACE = transarterial chemoembolization; NS = non-significant difference; PVT = portal vein thrombosis/invasion.

was limited but these appeared similar and consisted of leukopenia, transaminase elevation and deterioration in liver function.

A subsequent report after longer follow-up suggested a non-significant difference in survival. The 1-, 2- and 3-year survivals for the farmorubicin group were 69, 44 and 33%, respectively, and 73, 54 and 37%, respectively, for the doxorubicin group [24]. A retrospective subgroup analysis in which patients were classified as low or high risk [based on a combination of pre-treatment AFP level (log scale), tumor encroachment and Child's classification] suggested improved survival in low-risk patients with doxorubicin. Side-effects were similar between treatment groups. An additional CGLCJ study involved 77 patients randomized to TAE including either farmorubicin or adriamycin. There was no significant difference between the treatments [25].

Chang *et al.* evaluated the efficacy of cisplatin as a component of hepatic chemoembolization [26]. During 1991–1993, 22 Chinese patients received TAE including lipiodol and cisplatin (50 mg) versus 24 patients who received embolization (including lipiodol) without cisplatin. The mean number of treatments was approximately 3 in both groups. One- and 2- year survival was 52.5 and 26.2% for those receiving cisplatin versus 72.5 and 39.5% for control. There was no statistically significant difference. Thirteen percent of patients had diffuse tumor. Severe vomiting occurred more frequently in the patients receiving cisplatin.

In 2002, Chen *et al.* reported results of a trial comparing varied doses of lipiodol as a component of TACE [27,28]. In total, 473 patients were randomized to receive either high-dose lipiodol (at least 20 cm^3 or greater of iodized oil during the first TACE treatment) versus a lower dose (5–15 cm^3). Among the patients with Child–Pugh Class B liver function, high-dose lipiodol was associated with more significant hepatotoxicity. Survival was reported by subsets only. High-dose lipiodol was associated with improved survival in patients with Child–Pugh Class A liver function. One-, 2- and 3-year survival for patients with Child's A liver function was 79.2, 51.8 and 34.9% for the high-dose group, and 59.1, 26.7 and 14.9% for the low-dose group.

Conclusion

With regard to chemoembolization-based therapy in HCC, there is no clear evidence to suggest optimal

chemotherapeutic agents nor their dosages. Doxorubicin may confer superior antitumor effect (relative to farmorubicin), but its impact on long-term survival is unlikely to be significant. Higher doses of lipiodol may confer a survival benefit in patients with Child–Pugh Class A liver function. Unfortunately, these studies did not incorporate statistical power into their design. Reporting of untoward effects, duration of actual treatment and duration of follow-up was also incomplete.

Hepatic artery embolization versus hepatic artery chemotherapy

We identified two studies that compared chemoembolization to hepatic artery chemotherapy without embolization (see Table 3). Lu *et al.* randomized 52 subjects to receive either TACE (including lipiodol) or arterial chemotherapy and lipiodol without embolization [28]. Patients were categorized as type I (defined as Child–Pugh Class A and B liver function) or type II (Child–Pugh Class C or portal vein invasion or diffuse hepatic tumor). Survival was reported by subset analysis only. Two-year survival for type I (low-risk) patients was 40% for those receiving chemoembolization and 47% for those receiving arterial chemotherapy/lipiodol without embolization; these differences were not statistically significant. For type II (high-risk) patients, 1- and 2-year survival rates for the embolization group were 7 and 0%, respectively; 1- and 2-year survival for the lipiodol-chemotherapy group were 28 and 14%, respectively ($p < 0.05$).

In 1995, Hatanaka *et al.* conducted a three-arm trial comparing hepatic chemoembolization (with and without lipiodol) to hepatic artery chemotherapy [29]. Between 1986 and 1991, 429 patients were enrolled and 272 received randomized therapy. Reported results were difficult to interpret because patients who elected to receive subsequent therapies off-protocol were excluded from analysis; additional patients with advanced disease receiving hepatic chemotherapy without randomization were also discussed. Nonetheless, 60 randomized patients received TACE (including cisplatin, doxorubicin and FUDR), 78 underwent TACE (including lipiodol and chemotherapy as above) and 134 received hepatic artery lipiodol and chemotherapy (as above) without embolization. Mean number of treatments per patient ranged between 2.3 and 2.8 (depending upon treatment arm). One-, 2-, 3- and 5-year survival rates for those receiving TACE without lipiodol were 80, 65, 49 and 28%, respectively. Survival for those receiving TACE including lipiodol was 86, 55, 35 and 26% at 1, 2, 3 and 5 years. Differences between theses arms were not statistically significant. Survival for those receiving chemotherapy and lipiodol (without embolization) at 1, 2, 3 and 5 years was 66, 50, 36 and 18%. Survival on this arm was statistically inferior relative to the groups receiving embolization as a component of therapy.

Conclusion

The limited number of interventions comparing arterial embolization to non-embolization-based locoregional therapy prevents definitive conclusion. In patients with less advanced disease, embolization (with or without additional agents) likely is more effective than hepatic artery chemotherapy (including lipiodol) without embolization. This was demonstrated in the Japanese trial, in which nearly one-half of patients had unifocal (solitary) HCC at presentation. As demonstrated by Lu *et al.*'s results, embolization is unlikely to confer benefit (and is likely deleterious) in patients with advanced tumor (including portal venous invasion) and in patients with marked hepatic dysfunction [28].

Hepatic artery embolization utilizing different technical embolization methods

In 1998, Zheng *et al.* evaluated the effect of a Chinese herb comprised of starch mucagel and a volatile oil known as bletilla striata as a vascular embolizing agent [30]. Fifty-six patients undergoing hepatic artery embolization were treated with bletilla striata and 50 patients were treated with the more widely utilized gelfoam particles. The authors found a more significant decrease in AFP and tumor shrinkage in the group receiving the medicinal herb. Treatment was also better tolerated and was given for a longer duration (7 months). Survival at 1, 2 and 3 years for the bletilla group was 82, 45 and 34% versus 49, 31 and 16% for those embolized with gelfoam; this difference was statistically significant. Toxicity was reportedly similar between the embolization methods. However, the authors cautioned that safe use of bletilla striata embolization requires highly selective arterial catheterization; further explanation was not provided.

Kwok *et al.* investigated the use of autologous blood clot as an embolizing agent [31]. One hundred patients with Child–Pugh Class A or B liver function were randomized. Fifty-two patients received TACE via autologous clot every 6 weeks. Forty-eight patients received the TACE with the more commonly utilized gelfoam. There was no difference in survival. Side-effects were similar in both groups, and included frequent fever, vomiting and abdominal pain.

Conclusion

Very little randomized data exists regarding optimal physical means of hepatic arterial embolization. The studies above suggest that alternate mechanisms are feasible and at times may result in therapeutic differences (see Table 4). There is no evidence-based consensus regarding ideal physical agents for embolization-based therapy in HCC.

Table 3 Hepatic artery embolization versus hepatic artery chemotherapy

Publication	Intervention	Mean no. of sessions	Survival			Liver disease	Tumor extent	Comment/misc.
			Medn	1-year	2-year	Sign			
Lu	*Type I (low risk)*							
Chin Med J 1994	TACE (lipiodol + cisplatin 40–50 mg + doxorubicin 40–50 mg + mitomycin 10 mg): $n=10$	2		60%	40%	NS	Child's A 13% Child's B 60%	7% solitary 60% multifocal	Data reported for low/high-risk groups separately
	Hepatic artery lipiodol and chemotherapy (agents as above): $n=14$	2		68%	47%	$p<0.05$	Child's C 27%	or massive 23% diffuse	Type I: Child's A or B, no PVT, nodular or massive tumor
	Type II (high risk)								Type II: PVT or Child's C or diffuse tumor
	TACE (agents as above): $n=14$	2		7%tvs	0%				
	Hepatic artery lipiodol and chemotherapy (agents as above): $n=14$	2		28%	14%				
Hatanaka	TACE (cisplatin 50–100 mg + doxorubicin	2.8		80%	65%	$p<0.02$	17% HBV	49% solitary	No significant survival difference between embolization arms; non-embolization arm survival was inferior to both TACE arms.
Radiology 1995	20–40 mg + FUDR 3–5 g): $n=60$						Child's A 9%	43% multifocal	
	TACE (chemotherapy as above) + lipiodol: $n=78$	2.3		86%	55%		Child's B 28%	or massive	
	Hepatic artery chemotherapy (as above) + lipiodol: $n=134$	2.4		66%	50%			6% diffuse	

HCV = hepatitis C virus; HBV = hepatitis B virus; TAE = transarterial embolization; TACE = transarterial chemoembolization; NS = non-significant difference; PVT = portal vein thrombosis/invasion.

Hepatic artery-based therapy with or without local immunotherapy

In 1991, Tang *et al.* evaluated hepatic artery chemotherapy and low-dose external bean radiotherapy with addition of a bacterial vaccine (MBV) derived from *Streptococcus pyogenes* and *Serratia marcescens* [32]. In this study, 48 patients were randomized to receive intra-arterial cisplatin and radiotherapy with or without MBV via a surgically implanted hepatic artery catheter. The vaccine was infused daily or every other day through the hepatic arterial catheter. Regional radiotherapy was also given on days 1, 2 and 3, and alternated with arterial cisplatin (20 mg/day) on days 8, 9 and 10. This cycle was usually repeated 2–4 times. Survival at 1, 2 and 3 years was 59, 41 and 41% for the MBV group, and 39, 25 and 20% for the controls, respectively ($p = 0.01$, $p = 0.09$ and $p = 0.07$). Side-effects included transient chills and fevers immediately following the MBV injection. An analysis of macrophage activity in those receiving the MBV injection increased, but was not statistically different from those who did not receive the injection. The authors concluded that they considered MBV a potentially useful treatment.

In 1997, Lydigakis *et al.* compared hepatic artery chemoembolization including interferon (IFN)-γ and interleukin (IL)-2 to hepatic artery chemoembolization alone [33]. In total, 193 predominantly Greek patients considered ineligible for surgical resection were randomized. Ninety-one patients received hepatic artery chemoembolization (including lipiodol, mitomycin, carboplatin and mitoxantrone) and 102 patients received similar therapy with the addition of IL-2 and IFN-γ via two arterial catheters inserted into the splenic and hepatic arteries. Treatment was continued every month for the first year and every 2 months for the subsequent years. All patients had tumor involving over one-half of the liver volume. Overall survival was significantly improved in the group receiving immunotherapy (22.3 versus 10.2 months, reported as mean survival). Side-effects were described as minimal. The authors noted an improvement in cytopenias and esophageal varices for those patients in whom splenic artery infusion resulted in arterial occlusion, although specific results for this were not quantified.

An additional study by Chung *et al.* in which the addition of s.c. IFN-α to hepatic artery cisplatin resulted in a survival benefit (versus cisplatin alone and versus supportive therapy) is discussed in Part II of this report [34].

Conclusion

The addition of immunotherapy to hepatic artery-based treatments may confer a survival benefit; the small number of trials precludes definitive assessment (see Table 5). Trials utilizing immunotherapies (including activated lymphocyte infusions, interferons and addition

Table 4 Hepatic artery embolization with different technical embolization methods:

Publication	Intervention	Mean no. of session	Survival				Liver disease	Tumor extent	Comment/misc.
			Mean*	1-year	2-year	Sign			
Zheng *Chin Med J* 1998	TACE (carboplatin 500 mg, 5-FU 1000 mg, mitomycin C 10 mg) + bletilla striata: $n=56$	2.1	20 m	81%	45%	$p<0.05$	7% Okuda I 83% Okuda II 10% Okuda III	76% multifocal 24% diffuse	Significance for survival reported as three separate values at 1, 2 and 3 years
	TACE (carboplatin 500 mg, 5-FU 1000 mg, mitomycin C 10 mg) + gelfoam powder: $n=50$	4.1	16 m	49% ($p<0.05$)	31% ($p<0.01$)				
Kwok *J Hepatol* 2000	TACE (cisplatin 10–20 mg) + gelfoam: $n=52$		330 d	~38%	~23%	NS	52% HCV 44% HBV 32% Okuda I 64% Okuda II 3% Okuda III	43% solitary 28% multifocal 16% diffuse Median tumor 8 cm	
	TACE (cisplatin 10–20 mg) + autologous blood clot: $n=48$		338 d	~35%	~21%				

HCV = hepatitis C virus; HBV = hepatitis B virus; TAE = transarterial embolization; TACE = transarterial chemoembolization; NS = non-significant difference; PVT = portal vein thrombosis/invasion; d = days; m = months; ~ indicates approximate value extrapolated from Kaplan–Meier curve (actual statistic not reported); *mean survival (median not provided).

Table 5 Hepatic artery-based therapy with or without immunotherapy

Publication	Intervention	Mean no. of *sessions*	Survival				Liver disease	Tumor extent	Comment/misc.
			Medn	1-year	2-year	Sign			
Lygidakis *Hepatogastroenterology* 1997	TACE (carboplatin 2 mg/kg + mitomycin 0.2 mg/kg + mitoxantrone 0.2 mg/kg): $n=91$		10 m*			$p<0.005$	79% Okuda I 21% Okuda II	Tumor involved >60% liver surface in all patients	
	TACE (chemotherapy as above) to hepatic and splenic art. + IFN-γ + IL–2: $n=102$		22 m*						
Tang *Med Oncol Tumor Pharmacother* 1991	TACE (cisplatin 20 mg), radiotherapy (median 3600 rad), + MBV (mixed bacterial vaccine): $n=25$		20 m	59%	41%	NS ($p=0.01$–0.09)	64% HBV	mean tumor: 6–7 cm	Significance for survival reported as three separate values at 1, 2 and 3 years
	TACE (cisplatin 20 mg) + radiotherapy (median 3600 rad): $n=23$		14 m	39%	25%				

HCV = hepatitis C virus; HBV = hepatitis B virus; TAE = transarterial embolization; TACE = transarterial chemoembolization; NS = non-significant difference; m = months; *mean survival (median not provided).

of interferons to hepatic arterial therapy) have been associated with benefit in the adjuvant setting [35–37]. Additional investigations will hopefully clarify the role of such therapies in conjunction with hepatic arterial therapy in unresectable HCC.

Overall conclusions regarding hepatic arterial embolization-based therapies in HCC with respect to the randomized literature

(i) Chemoembolization for unresectable HCC confers a significant survival benefit. Patients for whom TACE is likely to be helpful are those with relatively preserved hepatic function (i.e. Child–Pugh Class A and selected Child–Pugh Class B liver dysfunction), modest tumor burden (i.e. absence of portal vein invasion, solitary or otherwise limited nodular or encapsulated tumors) and preserved performance status.

(ii) The positive results of the recently reported trials suggest that chemoembolization (TACE) may confer a more significant benefit than embolization without iodized oils or anticancer agents (TAE), although the number of trials in which these therapies have been compared is limited.

(iii) Embolization is potentially harmful in patients with portal vein thrombosis (invasion), Child–Pugh Class C liver dysfunction or diffuse tumor, especially if HCC is involving a majority of the liver volume. Patients with these disease characteristics may be considered for arterial therapy without embolization;

studies investigating such approaches are discussed in Part II of this review.

(iv) Embolization-based therapy appears to confer greater benefit than hepatic artery infusion of anticancer drugs or lipiodol without embolization (at least in patients with relatively limited tumor and preserved hepatic function), although very few investigators have prospectively studied this question.

(v) Recent studies in which chemoembolization was associated with a survival benefit employed sequential treatments, and utilized combinations of lipiodol and either cisplatin or doxorubicin.

(vi) There is limited information regarding optimal material for embolization, schedules of treatment and chemotherapy doses. No randomized trials have prospectively tested the utility of different types or sizes of embolization particles; there is no literature regarding the optimal degree of vascular occlusion required for safe and efficacious embolization.

(vii) Addition of immunotherapy to hepatic artery-based treatments has demonstrated potential for enhanced efficacy in a small number of studies; this represents a promising direction for future investigations.

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