Therapy for unresectable hepatocellular carcinoma: review of the randomized clinical trials—II: systemic and local non-embolization-based therapies in unresectable and advanced hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is not only common, but often presents at a stage when potentially curative therapies are not feasible. Although hepatic artery chemoembolization likely confers survival benefit in unresectable HCC, the associated toxicities are substantial and warrant investigation of more efficacious and safe therapies. Many patients who present with unresectable HCC are not chemoembolization candidates, either because of extensive disease or severely impaired hepatic function. We reviewed 44 randomized trials investigating non-embolization-based therapies in unresectable HCC. Hepatic artery infusion of [^{131}I]lipiodol appears safe; initial studies suggest a survival benefit and efficacy comparable to more toxic embolization-based therapies. Some cytotoxic chemotherapy may confer a modest survival benefit in advanced HCC (including oral fluoropyrimidines, and hepatic arterial or i.v. cisplatin and doxorubicin). Tamoxifen does not confer survival benefit, either in advanced or limited HCC. Other therapies warranting further study include interferon (in optimally cytoreduced HCC), megestrol in patients with variant estrogen receptors, octreotide and pravastatin. More adequately powered, rigorously conducted studies will hopefully identify useful chemo-, radio-, immuno-, embolization-based and biologically targeted therapies during the next decade. *Anti-Cancer Drugs* 15:439–452 © 2004 Lippincott Williams & Wilkins.

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Introduction and purpose of review

The prognosis for patients with unresectable HCC in whom hepatic artery embolization is not feasible is especially limited. Median survival in patients whose tumor invades the main portal vein is approximately 3 months; survival for those with metastatic disease is generally less than 6 months [1,2]. Responses to systemic chemotherapy are infrequent and there exists considerable skepticism as to the value of non-embolization-based systemic therapy [3]. Nonetheless, investigators have sought to delineate potential benefits of systemic therapies; these efforts are detailed below. Because of the lack of consensus regarding standards of care in advanced HCC, because of disparate results from the limited number of HCC studies and because previous reviews have excluded many trials (largely because of methodologic lapses), we have reviewed randomized trials investigating systemic therapy in unresectable HCC [4,5].

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 406 articles. Earlier review papers and textbook chapters were also evaluated [6,7].

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

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groups as follows: (i) neo-adjuvant and adjuvant trials in surgically resectable HCC (this was the subject of our recent review) [8], (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.

With regard to systemic and local non-embolization-based therapies in unresectable HCC, 44 articles met criteria and are reviewed below. The 44 trials investigating aspects of systemic therapy included 17 from Asia (Hong Kong $n = 8$, Japan $n = 8$, Korea $n = 1$), four from Africa (South Africa $n = 3$, Zimbabwe $n = 1$), five collaborations between investigators in the US and South Africa, one from the US and 17 from Europe (Spain $n = 4$, Italy $n = 3$, France $n = 3$, UK $n = 3$, Greece $n = 3$, Finland $n = 1$). A significant survival benefit was reported in 34% (15 of 44). In addition, several additional trials reported superiority of one regimen based on comparable efficacy and significantly reduced toxicity relative to the alternate regimen. Three studies randomized over 200 patients, seven involved 100–200 subjects, 18 randomized 50–100 patients and 16 (36%) involved fewer than 50 patients. In 11 of 44 (25%) of these investigations, sample size was determined by previously determined statistical endpoints; the remainder were not powered to demonstrate specific differences in outcomes. The majority of investigations were analyzed in an intention-to-treat fashion (39 of 44, 89%). Side-effects were reported in 41 (93%), although in only six studies (14%) was complete grading of untoward effects provided; three reports did not describe side-effects.

Trials comparing cytotoxic chemotherapy (systemic or hepatic artery) versus no anticancer therapy (Table 1)

During the 1980s, Lai *et al.* randomized 106 unresectable HCC patients to receive i.v. doxorubicin versus no antitumor therapy [9]. Doxorubicin was associated with 25% treatment-related mortality (neutropenia and cardiotoxicity) and universal emesis. Survival in the treatment group was somewhat improved, with medians of 10.6 weeks versus 7.5 weeks ($p = 0.036$). The authors were nonetheless skeptical regarding the utility of doxorubicin for future study, both because of toxicity and a poor (3%) response rate. It is likely that the inclusion of patients with severe hepatic dysfunction contributed to the marked toxicity; the trial predates the availability of potent antiemetic drugs and leukocyte-stimulating factors. Despite the uncertainties resulting from this trial, doxorubicin has been a frequently utilized

Table 1 Cytotoxic chemotherapy (systemic or hepatic artery) versus no anticancer therapy

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	1-year	2-year	Sign			
Lai *Cancer* 1988	Doxorubicin 60 mg/m^2 i.v. q3 wk (dose adj. ↑↓; 75 mg/m^2 max.): $n=60$	10.6 wk			$p<0.036$	Included jaundiced pts	Not stated	25% treatment related mortality in doxorubicin arm
	No anticancer rx: $n=46$	7.5 wk						
Ishikawa *J Gastroenterol Hepatol* 2001	Tegafur/Uracil, enteric-coated, 400 mg p.o. b.i.d.: $n=28$	12 m	55%	37%	$p<0.01$	65% Child's B 21% Child's C	Stage IV-A 42% PVT	Minimal GI and hepatic toxicity
	No anticancer rx: $n=28$	6 m	6%	0%				
Chung *Cancer* 2000	Cisplatin 2 mg/kg (hep. art.) q8 wk + IFN-α2b 3×10^6 IU/m^2 s.c. t.i.w.: $n=19$	19 wk	27%		$p<0.05$ $p<0.01$	43% Child's B 10% Child's C	69% PVT 40% met 20% infiltrative	Universal flu-like syndrome (IFN)
	Cisplatin 2 mg/kg (hep. art.) q8 wk: $n=23$	11 wk	9%					
	No anticancer rx: $n=26$	5 wk	0%					
Madden *Gut* 1993	Epirubicin 60 mg/m^2 + lipiodol 6 ml (hep. art.) q4 wk: $n=25$	48 d			NS	Included ECOG PS 3, Okuda III and jaundiced pts	Not stated	
	No anticancer rx: $n=25$	51 d						

PVT = portal vein invasion/thrombosis; met. = metastatic; hep. art. = hepatic artery; wk = week; m = month; d = day; NS = non-significant; PS = performance status; IFN = interferon; rx = therapy.

agent in advanced HCC during studies published during the past decade.

More recently, Ishikawa *et al.* randomized 56 patients with stage IV-A HCC to oral tegafur/uracil versus supportive care; 42% of patients had tumor invasion of the portal vein and over 85% had either Child–Pugh Class B or C liver dysfunction. Tegafur/uracil was associated with limited GI and hepatic toxicity. Median survival was 12 months for the treatment arm and 6 months for the control group [10].

Chung *et al.* randomized 68 Korean patients with HCC and either portal vein invasion or metastases to receive either daily interferon (IFN)-α and periodic hepatic artery cisplatin, hepatic artery cisplatin only, or supportive care [11]. Over two-thirds of patients had tumor invasion of the portal vein. Over 50% had either Child–Pugh Class B or C liver dysfunction although patients with significantly elevated bilirubin or low albumin were excluded. Toxicities included near-universal flu-like syndrome (IFN) and transient nausea in 50% (cisplatin), but were not severe or treatment limiting. Median survival for those receiving combined therapy was 19 versus 11 weeks for those receiving hepatic artery platinum and 5 weeks for supportive care only.

An earlier trial by Madden *et al.* compared hepatic artery lipiodol and epirubicin versus symptomatic therapy [12]. There was no survival difference between the two groups. The trial incorporated few exclusion criteria (i.e. patients with jaundice were enrolled) and included patients with ECOG performance status 3 and Okuda stage III disease. Median survival for either arm was less than 2 months.

Conclusion

The limited number of trials in advanced HCC in which chemotherapy has been compared to supportive care in a randomized setting prevents definitive conclusion. The earlier studies demonstrate that patients with significant jaundice or other stigmata of advanced organ dysfunction do not benefit from chemotherapy and experience frequent, severe toxicity. The trials reported by Ishikawa *et al.* and Chung *et al.* were specifically tailored to patients with extensive HCC. Both investigations suggest that cytotoxic agents can be administered with limited toxicity, even in the setting of moderate (but not extreme) hepatic dysfunction, and that these agents may confer survival benefit in the setting of poor-prognosis HCC.

Trials comparing different systemic (i.v.) chemotherapy regimens

One of the earliest randomized studies in unresectable liver cancer was an ECOG study in which 168 patients were randomized to receive either oral 5-fluorouracil (5-FU), oral 5-FU plus streptozotocin, oral 5-FU plus methyl-CCNU or doxorubicin [13]. The authors included patients with cholangiocarcinoma and patients with jaundice. A majority of subjects had ECOG performance status of 2–3. Patients receiving single-agent therapy (either 5-FU or doxorubicin) experienced less gastrointestinal side-effects than those receiving combination treatments. Responses were infrequent and were mostly seen in the group receiving doxorubicin (16%). Survival was limited for all groups (median 14 weeks for a North American subset), but appeared significantly lower in the group receiving oral 5-FU only. The authors concluded that doxorubicin demonstrated the best potential for benefit, both because of efficacy and a limited toxicity profile [14].

Choi *et al.* compared doxorubicin monotherapy versus a combination of 5-FU, methotrexate, cyclophosphamide and vincristine in 39 randomized HCC patients [15]. Many patients had abnormal bilirubin and median performance status was low (Karnofsky 50%). Responses were assessed clinically (i.e. resolution of hepatomegaly). Toxicity was not markedly different between the two groups and survival was superior in the doxorubicin group (13 versus 6.5 weeks). An additional randomized comparison by Melia *et al.* suggested that doxorubicin conferred a survival advantage over etoposide and also did not require hospitalization for administration [16].

Additional randomized comparisons during the 1980s and 1990s included the following: mitoxantrone versus cisplatin [17], doxorubicin versus 5-FU + meCCNU versus 5-FU + streptozotocin versus 5-FU + meCCNU + doxorubicin [14], neocarzinostatin versus m-AMSA versus doxorubicin [18], combinations of doxorubicin/VM-26/5-FU versus m-AMSA/VM-26/5-FU [19], combinations of mitomycin C/carboquone/5-FU/OK-432 versus mitomycin-C/5-FU/doxorubicin [20], acivicin versus 4-deoxydoxorubicin [21], epirubicin versus doxorubicin [22] and nolatrexed versus doxorubicin [23]. None of these investigations in advanced HCC demonstrated a survival benefit of one drug or regimen versus another nor did any drug or regimen demonstrate a toxicity profile preferable to doxorubicin. Hence, doxorubicin has remained a viable standard in the care of patients with advanced HCC, although its efficacy is limited and it is contraindicated in patients with significantly elevated bilirubin or other evidence of advanced hepatic failure. Emesis occurs less frequently in the current era of potent antinausea therapy, but potential for doxorubicin toxicity remains significant.

Trials comparing hepatic artery chemotherapy with systemic chemotherapy or investigating different types of hepatic artery chemotherapy (Table 2)

During the late 1980s, Kajanti *et al.* randomized 20 unresectable HCC patients with preserved liver function

to receive either i.v. or hepatic artery 5-FU and epirubicin given every 4 weeks [24]. Patients receiving arterial therapy had substantially less leukopenia, alopecia and emesis than those receiving i.v. treatment. Survival was similar in the two groups (15.2 months median for arterial therapy; 13.8 months for those receiving i.v.); the small number of patients treated precludes definitive conclusion.

Tzoracoleftherakis *et al.* randomized 72 unresectable HCC patients to receive either i.v. or hepatic artery doxorubicin (by means of an implanted catheter) [25]. There were significant complications related to the implanted port, such that approximately 14% of patients who were randomized to hepatic arterial therapy never received treatment; these complications included pouch infection, arterial aneurism and duodenal fistula. Other toxicities were comparable. The analysis was not conducted in an intention-to-treat manner. Survival was similar between the two arms (median 7 months for the arterial group, 6.5 months for i.v. treatment).

Yoshikawa *et al.* randomized 36 patients with unresectable HCC to receive epirubicin via periodic hepatic arterial infusion, either as monotherapy or in combination with lipiodol [26]. Over 80% of patients had stage IV-A tumor (LCSGJ criteria) and one-third had portal vein thrombus. All patients were treated by means of an implanted hepatic artery catheter. A small number of patients randomized to receive epirubicin were not included in the analysis because of immediate complications, including port malfunction. Combined therapy with lipiodol resulted in more frequent nausea, vomiting, fever and abdominal pain than did epirubicin. A higher rate of response was reported amongst those receiving epirubicin–lipiodol (42 versus 12%) although it is not clear how these responses were determined, given that lipiodol obscures tumor assessment on subsequent CT imaging. Survival was higher in those receiving combination therapy (73 versus 43% 1-year survival) although these differences did not reach statistical significance ($p = 0.09$). A higher percentage of patients in the group receiving epirubicin monotherapy had portal vein thrombosis and elevated AFP levels at baseline.

Conclusion

The limited number of studies and small number of patients preclude definitive assessment regarding the utility of hepatic artery chemotherapy. Chemotherapy delivered via the hepatic artery may be less toxic than when given i.v., although no survival benefit has been demonstrated. The potential for toxicity from implanted arterial ports is also significant. The inclusion of lipiodol with arterial chemotherapy may result in more toxicity and has shown potential survival benefit in a single, small trial. Because of the toxicities often encountered with systemic chemotherapy in HCC patients, intra-arterial therapy remains attractive. At our center, HCC patients with portal thrombus are offered hepatic arterial therapy, given intermittently without placement of an arterial port. We have experienced minimal toxicity with this approach and observed significant periods of disease stability; responses are infrequent. It is possible that hepatic artery chemotherapy confers a survival advantage in locally advanced HCC relative to no therapy or ineffective therapy; a clinical trial to assess this is being planned.

Trials investigating systemic therapy following hepatic artery embolization versus embolization without systemic therapy (Table 3)

Clinical trials evaluating hepatic artery embolization-based therapies are discussed in the preceding companion paper. Recent studies and meta-analyses suggest that hepatic embolization and chemoembolization confer

Table 2 Hepatic artery chemotherapy versus systemic chemotherapy or different types of hepatic artery chemotherapy

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	1-year	2-year	Sign			
Kajanti *Am J Clin Oncol* 1992	Epirubicin 40–60 mg/m^2 + 5-FU 800 mg/m^2 (hepatic artery) q4 wk: $n=10$	15.2 m			NS	80% Primack Stage I–II	55% Bengmark II 45% Bengmark III	
	Epirubicin 40–60 mg/m^2 + 5-FU 800 mg/m^2 i.v. q4 wk: $n=10$	13.8 m						
Tzoracoleftherakis *Hepatogastroenterology* 1999	Doxorubicin 50 mg/m^2 q3–4 wk via hepatic artery: $n=30$	7 m	7%		NS	Not stated	Not stated	
	Doxorubicin 50 mg/m^2 q3–4 wk i.v.: $n=34$	6.5 m	3%					
Yoshikawa *Cancer Chemother Pharmacol* 1994	Hepatic artery epirubicin 70 mg + lipiodol 2–3 ml q3 wk: $n=19$		73%	35%	$p=0.09$	Not stated	81% LCSGJ stage IV-A 33% PVT	
	Hepatic artery epirubicin 70 mg q3 wk: $n=17$		43%	0%				

LCSGJ = Liver Cancer Study Group of Japan; m = month; w = wk; PVT = portal vein invasion/thrombosis; NS = non-significant.

a survival benefit. Although there are no studies investigating the role of i.v. chemotherapy following TACE, several investigators have evaluated the role of oral cytotoxic and other therapies in this setting.

Specific studies

Ikeda *et al.* randomized 40 good performance status, predominantly HCV-infected patients undergoing hepatic arterial chemoembolization (TACE) to receive oral tegafur/uracil (UFT) or no therapy following TACE [27]. The groups were well matched with regard to tumor extent and liver disease. More patients in the TACE-only arm had complete necrosis of tumor in the 3–6 months following initial therapy. While the specific side-effects attributed to tegafur/uracil were minimal, more patients in this arm of the trial developed ascites or encephalopathy (95 versus 70%) and decompensation of cirrhosis (30 versus 5%) during the first 6 months following initial therapy. It was not certain as to whether this decompensation was related to tumor progression or therapy. There was a non-significant trend towards worse survival in the patients receiving UFT following TACE (median survival 23 versus 28 months).

Ikeda *et al.* also studied the addition of oral deoxy-5-fluorouridine (5-DFUR) in 40 patients following TACE [28]. As in the prior trial, there were minimal side-effects attributed specifically to the oral agent. Responses to TACE were similar in both arms and there was no difference in rates of ascites, encephalopathy or other manifestations of cirrhotic decompensation. Survival was similar between the two groups (65 and 66% at 2 years); median survival had not been reached at the time of analysis.

Kawata *et al.* randomized 83 patients undergoing TACE to receive therapy with oral pravastatin or no additional treatment [29]. (All patients received oral 5-FU for 2 months following TACE.) Patients were predominantly HCV infected and 70% had Child–Pugh Class B liver dysfunction. Pravastatin was tolerated well; no patient required discontinuation for transaminase elevation. The extent of tumor eradication following TACE was not described. Survival was significantly improved on the pravastatin arm (median 18 versus 9 months for those receiving TACE and oral 5-FU only).

Conclusion

Assessing the impact of systemic therapy following TACE is difficult in small clinical trials because of the very diverse responses seen following embolization therapy. A benefit conferred by embolization could result in a benefit incorrectly attributed to subsequent systemic therapy. Hence, larger trials are required to definitively assess the impact of therapies following TACE. No clear benefit was observed in the two trials assessing oral 5-fluoropyrimidine therapy. The inclusion of potentially resectable patients in these trials—and their small size—would not enable recognition of a small or moderate benefit; additional trials will hopefully include a more homogenous group of unresectable patients, and numbers sufficient to test a reasonable hypothesis.

The potential for pravastatin, an HMG-CoA reductase inhibitor to impact upon cancer cell signal transduction has been demonstrated in preclinical models [30]. Kawata *et al.*'s results are encouraging, both in terms of potential survival advantage and because of the relative safety of pravastatin in HCC relative to cytotoxic therapies. Agents such as HMG-CoA reductase inhibitors, cyclooxygenase inhibitors, and peroxisome proliferator-activated receptor γ ligands (thiazolidinediones, currently used as oral antidiabetic therapy) have shown significant potential to inhibit cancer growth in cell and

Table 3 Systemic therapy following hepatic artery embolization versus embolization without systemic therapy

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	2-year	3-year	Sign			
Ikeda *Am J Clin Oncol* 1995	TACE + UFT (200 mg tegafur; 448 mg uracil) p.o. qd: $n=20$ TACE: $n=20$	23 m 28 m		21% 48%	NS	90% HCV 13% HBV	18% unifocal 45% bilateral No PVT	Included potentially resectable patients
Ikeda *Am J Clin Oncol* 1997	TACE + 5-DFUR 400 mg p.o. qd: $n=20$ TACE: $n=20$		65% 66%	65% 50%	NS	75% HCV 28% HBV 90% Okuda I	13% unifocal 45% bilateral 8% PVT	Included potentially resectable patients
Kawata *Br J Cancer* 2001	TACE + 5-FU 200 mg p.o. qd × 2 m + pravastatin 40 mg p.o. qd: $n=41$ TACE + oral 5-FU 200 mg p.o. qd × 2 m: $n=42$	18 m 9 m			$p=0.006$	82% HCV 11% Child's A 70% Child's B	71% LCSGJ stage II–III 13% PVT 4% met.	

TACE = transarterial chemoembolization; m = month; NS = non-significant; PVT = portal vein invasion/thrombosis; met. = metastatic; LCSGJ = Liver Cancer Study Group of Japan; HBV = hepatitis B virus; HCV = hepatitis C virus.

animal investigations [31–33]. Because of their favorable toxicity profile, these drugs will hopefully be tested in HCC, both in advanced disease states and alongside established cytoreductive therapies.

Trials comparing immunotherapy versus no anticancer therapy or immunotherapy versus chemotherapy (Table 4)

During the late 1980's, Lai *et al.* randomized 71 good performance, predominantly hepatitis-B-infected patients with inoperable HCC to receive either IFN-α2a intramuscularly 3 days per week at a dose of 50×10^6 IU/m^2 versus placebo [34]. IFN caused universal flu-like symptoms, fatigue, persistent fever, and infrequent cytopenias and mental status alterations. One-third of patients required dose reductions. IFN induced a partial response in 31% of patients and was associated with improved median survival (14.5 versus 7.5 weeks for placebo; $p = 0.05$).

Llovet *et al.* randomized 58 predominantly HCV-infected patients with advanced HCC (one-third had portal vein invasion) to receive either IFN-α2b s.c. 3 days per week at a dose of 3×10^6 IU versus supportive care [35]. IFN toxicities included fatigue and cytopenias, and 48% of patients required discontinuation of therapy. IFN conferred a 7% partial response rate and was associated with an improvement in survival (58 versus 36% at 1 year) which did not achieve statistical significance. Because of limited tolerance, enrollment was terminated before the planned cohort (38 per arm) could be enrolled.

Also during the 1980s, Lai *et al.* enrolled 75 HBV-infected, good performance patients with unresectable HCC to receive either high-dose IFN-α via daily or thrice-weekly schemes (50×106 IU/m^2 i.m. t.i.w. or 18×10^6 IU/m^2 i.m. qd), or i.v. doxorubicin at 60–75 mg/m^2 every 3 weeks [36]. Toxicities for IFN included universal flu-like syndrome, fatigue and bone marrow suppression. Doxorubicin was associated with 25% fatal toxicity from both cardiac failure and neutropenic sepsis. The IFN regimens conferred significantly higher rates of response or stability relative to doxorubicin (69 versus 19%); however, there was no significant survival difference.

In 1995, Falkson *et al.* reported the results of a multicenter trial comparing IFN-β (90×10^6 U given i.v. for 10 consecutive days over a 21-day cycle) versus menogaril (an anthracycline derivative) given i.v. every 4 weeks [37]. Sixty-five patients were enrolled on this ECOG sponsored study, which was stopped before accrual was reached because of poor efficacy. Toxicity on both treatment arms was significant and included severe myelosuppression, which was fatal in two instances. There was no difference in time-to-progression or survival.

In the Korean trial discussed in a previous section, Chung *et al.* found that the addition of IFN-α conferred a survival

Table 4 Immunotherapy versus no anticancer therapy or immunotherapy versus chemotherapy

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	1-year	2-year	Sign			
Lai *Hepatology* 1993	IFN-α2a 50×10^6 IU/m^2 i.m. t.i.w.: $n=35$	14.5 wk			$p=0.047$	94% HBV 9–17% abnl BR	Not stated	IFN: universal flu-like syndrome, fatigue, fever
	Placebo: $n=36$	7.5 wk						
Llovet *Hepatology* 2000	IFN-α2b 3×10^6 IU s.c. t.i.w.: $n=30$		58%	36%	$p=0.14$ (NS)	78% HCV 60% Child's A	Not elig. for TACE 74% multinod. 38% PVT	
	No anticancer rx: $n=28$		36%	12%				
Lai *Br J Cancer* 1989	IFN-α (2a) 50×10^6 IU/m^2 i.m. t.i.w. or 18×10^6 IU/m^2 qd: $n=47$	8.3 wk			(NS)	88% HBV	NS	25% treatment related mortality in doxorubicin arm; 69% PR-SD rate in IFN arm
	Doxorubicin 60–75 mg/m^2 i.v. q3wk: $n=22$	4.8 wk						
Falkson *Am J Clin Oncol* 1995	IFN-β 90×10^6 IU i.v. qd × 10 d, q3 wk: $n=31$	11.1 wk			(NS)	Included jaundiced pts	NS	
	Menogaril 200–240 mg/m^2 i.v. q4 wk: $n=34$	23.1 wk						
Miyaguchi *Hepatogastroenterology* 2002	TACE + PEI + IFN-α2b 3×10^6 IU/m^2 t.i.w.: $n=22$	Not reached			$p<0.001$	100% HCV 47% Child's A 53% Child's B	Median < 3 cm 70% unifocal	All pts HCV-RNA < 0.5 meq/ml ('low HCV RNA')
	TACE + PEI: $n=24$	25 m						

TACE = transarterial chemoembolization; PEI = percutaneous ethanol injection; m = month; wk = week; NS = non-significant; HBV = hepatitis B virus; HCV = hepatitis C virus; PVT = portal vein invasion/thrombosis; met. = metastatic; multinod. = multifocal tumor.

benefit relative to monotherapy with hepatic artery cisplatin and that both therapies conferred a survival advantage over supportive care [11].

Recently, Miyaguchi *et al.* randomized 46 HCV-infected, limited-stage HCC patients undergoing combined hepatic arterial chemoembolization and percutaneous alcohol injection to receive either IFN-α (3×10^6 U thrice weekly) or no systemic therapy [38]. All patients had low HCV viral load (below 0.05 mEq/ml HCV-RNA) as enrollment criteria. Survival at 30 months was above 80% for the IFN group and approximately 20% for those receiving locoregional therapy only. There was no reported difference in rates of recurrence at the initial tumor site; however development of additional tumors was substantially reduced in the group receiving IFN. The authors conclude that the effects of IFN were predominantly chemopreventative. Other trials in cirrhotic patients without HCC and following surgical resection of HCC have also suggested a similar benefit from IFN-α [39–42].

Conclusion

Recent trials have suggested a benefit from low- to moderate-dose IFN-α both for HCC prevention in cirrhotic populations and prevention of HCC recurrence following resection of limited-stage HCC; this benefit may also extend to patients with limited-stage tumor who are treated with non-surgical locoregional therapies. There is inconclusive evidence regarding the utility of IFNs for treatment of advanced disease, although addition of IFN-α to chemotherapy may confer survival benefit. High-dose IFN has resulted in HCC regression as demonstrated by Lai *et al.*; however, the significant toxicities and uncertain survival benefit have not resulted in widespread use of these regimens.

Trials comparing radioisotope (^{131}I) therapy versus no anticancer therapy or other treatment modalities (Table 5)

Raoul *et al.* randomized 27 HCC patients with portal vein thrombosis and predominantly alcohol-induced liver disease to receive radioactive iodine conjugated to lipiodol ([^{131}I]lipiodol) via hepatic arterial infusion versus no anticancer therapy [43]. Patients enrolled in this study had significant liver disease (48% Child–Pugh class B liver function) and 75% had tumor invading the main portal trunk. [^{131}I]Lipiodol therapy was well tolerated and notable predominantly for transient asthenia. Accrual was stopped earlier than planned because of superior survival in the treatment group (6-month survival 48 versus 0%; $p < 0.01$). Although some of the patients in the control arm received some form of antitumor treatment (five received tamoxifen, one received 5-FU), it is unlikely that these therapies significantly influenced the results.

In a RTOG-sponsored trial during the 1980s, Order *et al.* randomized 98 patients with unresectable HCC to receive either [^{131}I]antiferritin antibody therapy given every 8 weeks (in conjunction with low-dose doxorubicin and 5-FU) versus more standard doses of doxorubicin and 5-FU given every 3 weeks [44]. All patients received induction external beam radiation (2100 cGy) and chemotherapy; crossover therapy was permitted upon progression. Toxicity was comparable in both arms and severe effects were predominantly related to

Table 5 Radionucleotide (^{131}I) therapy versus no anticancer therapy or other treatment modalities

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		6-m	1-year	2-year	Sign			
Raoul *J Nucl Med* 1994	[^{131}I]Lipiodol (60 mCi) via hepatic artery × 4 over 1 year: $n=14$	48%			$p<0.01$	81% etoh 48% Child's B 52% Child's A	75% main PVT 25% branch PVT	
	No anticancer rx: $n=13$	0%						
Order *Int J Radiat Oncol Biol Phys* 1991	[^{131}I]Antiferritin + doxorubicin 15 mg + 5-FU 500 mg q8 wk: $n=48$	No dif.			NS	Not stated	No met.	
	Doxorubicin 60 mg/m^2 + 5-FU 500 mg/m^2 q3 wk: $n=50$							
Bhattacharya *Cancer* 1995	[^{131}I]Lipiodol via hepatic artery: $n=11$	58%	25%	0%	NS	Child's A and B	No PVT	
	Lipiodol + epirubicin 75 mg/m^2 via hepatic artery: $n=17$	40%	25%	6%				
Raoul *Hepatology* 1997	[^{131}I]Lipiodol via hepatic artery × 5 over 18 m: $n=65$	69%	39%	22%	NS	74% etoh 75% Child's A	50% unifocal 24% tumor involving >50% of liver volume	27% life-threatening toxicity and 9% fatal toxicity in TACE arm
	TACE (including cisplatin 70 mg) × 5 over 18 m: $n=64$	66%	42%	22%				

TACE = transarterial chemoembolization; m = month; NS = non-significant; HBV = hepatitis B virus; HCV = hepatitis C virus; PVT = portal vein invasion/thrombosis; met. = metastatic; etoh = alcohol-induced liver disease; rx = therapy.

myelosuppression. No survival differences were seen between the two arms. Patients with elevated AFP had significantly diminished survival versus those with normal-range values. Of note, seven of 11 AFP-normal patients experienced response when [^{131}I]antiferritin was given after crossover, whereas no responses were seen in 15 patients with elevated AFP receiving crossover therapy. Responses to chemotherapy following crossover were rare.

Bhattacharya *et al.* randomized patients with unresectable HCC to receive either hepatic artery [^{131}I]lipiodol or hepatic artery lipiodol and doxorubicin [45]. Only 28 of 95 patients in their report had actually been part of a randomized intervention. Toxicity (predominantly fever, abdominal discomfort and leukopenia) was more frequent in the lipiodol–epirubicin arm. Survival was similar between the two treatments (both for randomized and non-randomized groups).

Raoul *et al.* also compared hepatic artery [^{131}I]lipiodol therapy to chemoembolization (including cisplatin) in 129 patients with predominantly alcohol-induced liver disease and Child–Pugh Class A liver dysfunction [46]. There was significant heterogeneity of tumor extent in this randomized French trial. One-half of the patients had unifocal tumor; however, 24% were reported to have tumor which involved over 50% of the liver volume. Toxicity was significantly higher in the patients undergoing chemoembolization and included liver dysfunction, pain, gastrointestinal bleeding or hemoperitoneum; 27% of these were considered life threatening and 9% were fatal. One-year survival was 39% for those receiving [^{131}I]lipiodol and 42% for those undergoing chemoembolization; there was no significant survival difference between the treatment groups.

In a recently reported trial by Brans *et al.*, the addition of low-dose i.v. cisplatin to hepatic artery [^{131}I]lipiodol was associated with improved rates of stability relative to [^{131}I]lipiodol without radiosensitizing chemotherapy. This trial is not discussed in detail because the results are presented as preliminary, and the small sample size ($n = 10$ for each group) is unlikely to enable identification of potential survival benefit [47].

Conclusion

Hepatic artery [^{131}I]lipiodol therapy in HCC has shown potential for benefit with consistently mild toxicities in several randomized HCC investigations. An adjuvant study following hepatic resection done by Lau *et al.* indicated significant post-surgical benefit such that randomization to supportive therapy was halted after interim analysis (although the authors' use of this early stopping rule has been questioned) [48,49]. The trial reported by Raoul in which [^{131}I]lipiodol was associated with significantly improved survival suggests that radiotherapy in HCC may confer benefit in more advanced disease states. The other studies detailed above confirm the potential for limited toxicity associated with [^{131}I]lipiodol and suggest that this modality is likely to be associated with fewer side-effects than other beneficial therapies, including chemotherapy and embolization-based treatments. Results from these initial trials utilizing [^{131}I]lipiodol warrant additional investigation with this agent.

Trials investigating hormonal therapy versus no therapy or other therapy

Tamoxifen-based therapy (Tables 6 and 7)

Because HCC is observed more frequently in males than females and because some HCCs express estrogen receptors, the use of tamoxifen or other low-toxicity hormonal agents was studied extensively during the late 1980s and 1990s. Initial case-control studies by Farinati *et al.* at the University of Padua suggested a potential survival benefit, although 50% of the deaths in the control arms occurred within 1 month of enrollment [50,51].

Martinez *et al.* in Barcelona randomized 36 predominantly HCV-infected patients with advanced HCC to receive tamoxifen (20 mg/day) versus no treatment [52]. Two-thirds of the subjects had either massive or diffuse tumor and 14% had Child–Pugh Class C liver dysfunction. The groups were equivalent in terms of baseline tumor extent and hepatic function, although a higher proportion of patients in the control arm developed complications of hepatic failure (bleeding, ascites or encephalopathy) during the study (81 versus 25%). Enrollment was terminated following a planned interim analysis which indicated superior survival in the tamoxifen arm (median survival was 261 versus 172 days; 1-year survival 48 versus 9%).

Elba *et al.* also noted a survival advantage in 11 HCC patients randomized to tamoxifen (60 mg/day) versus 11 receiving placebo (median survival 74 versus 52 weeks) [53]. Manesis *et al.* in Athens, Greece randomized 85 predominantly HBV-infected patients with unresectable HCC to receive either tamoxifen plus the LHRH analog triptorelin versus triptorelin and flutamide, versus placebo [54]. Although there were no differences in median survival, a higher 1-year survival and lower incidence of portal vein invasion in the group receiving tamoxifen led the authors to conclude that tamoxifen conferred survival benefit compared to antiandrogen therapy or placebo.

Summary of trials in which tamoxifen was associated with clinical benefit

The authors of several small studies (some of which included patients with advanced HCC and severe liver dysfunction) concluded that tamoxifen conferred a

Table 6 Tamoxifen-based hormonal therapy versus no therapy or other therapy: positive studies

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	1-year	2-year	sign			
Martinez *J Hepatol* 1994	Tamoxifen 10 mg b.i.d. p.o.: $n=20$ No therapy: $n=16$	261 d 172 d	48% 9%		$p<0.01$	86% HCV 50% Child's A	17% PVT 67% massive or diffuse	
Elba *Ital J Gastroenterol* 1994	Tamoxifen 60 mg qd p.o.: $n=11$ Placebo: $n=11$	74 w 52 w			$p=0.04$	82% Child's A 18% Child's B	Median tumor 5.8 cm	
Manesis *Hepatology* 1995	Tamoxifen 30 mg qd p.o. + Triptorelin 3.75 mg qm i.m.: $n=33$ Triptorelin 3.75 mg qm i.m. + Flutamide 250 mg t.i.d. p.o.: $n=23$ Placebo: $n=29$	282 d 112 d 127 d			$p<0.003$	62% HBV median BR = 2.9 mg/dl	Median tumor 9.7 cm	

d = day; w = week; m = month; NS = non-significant; HBV = hepatitis B virus; HCV = hepatitis C virus; PVT = portal vein invasion/thrombosis; met. = metastatic; etoh = alcohol-induced liver disease; BR = serum bilirubin.

Table 7 Tamoxifen-based hormonal therapy versus no therapy or other therapy: negative studies

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	1-year	2-year	Sign			
CLIP *Lancet* 1998	Tamoxifen 40 mg p.o. qd: $n=237$ No therapy: $n=240$	15 m 16 m	56% 57%		$p=0.54$	81.5% HCV 43% Child's A 38% Child's B	53% not eligible for locoregional rx.	5% discontinued TAM therapy because of side-effects
Castells *Gastroenterology* 1995	Tamoxifen 20 mg p.o. qd: $n=58$ Placebo: $n=62$	6 m 6 m	51% 43%	27% 29%	$p=0.75$	77% HCV	75% multinodular or massive	
Riestra *J Clin Gastroenterol* 1998	Tamoxifen 40 mg p.o. qd: $n=40$ Placebo: $n=40$		30% 38%		$p=0.31$	32% etoh 30% HCV 29% et + HCV 22% Okuda 3	60% multinodular or massive 23% PVT	
Chow *Hepatology* 2002	Tamoxifen 120 mg p.o. qd: $n=120$ Tamoxifen 60 mg p.o. qd: $n=74$ Placebo: $n=132$	2.2 m 2.1 m 2.7 m			$p<0.02$	43% Child's A 45% Child's B 13% Child's C 8% PS = 3 29% Okuda 3	Not stated	Tamoxifen associated with decreased survival
Liu *Am J Gastroenterol* 2000	Tamoxifen 30 mg p.o. qd: $n=61$ Placebo: $n=58$	44 d 41 d			$p=0.7$	78% HBV 14% Child's C 22% Okuda III	59% IV-A 22% met.	
Melia *Cancer Treat Rep* 1987	Doxorubicin 60 mg/m^2 q3 wk: $n=28$ Doxorubicin 60 mg/m^2 q3 wk + tamoxifen 10 mg p.o. b.i.d.: $n=25$	2 m 2.5 m			NS	40% HBV 10% etoh	Not stated	
Uchino *Am J Clin Oncol* 1993	Hepatic artery doxorubicin (26 mg/m^2) and cisplatin (60 mg/m^2) + oral 5-FU 150 mg/m^2 qd + tamoxifen 40 mg qd + medroxyprogesterone acetate 40 mg qd: $n=15$ Hepatic artery and oral chemotherapy (as above); no hormonal rx : $n=15$		83% 79%		NS	12% HBV 19% Child's A 69% Child's B	LCSG Japan III: 31% IV: 38%	

TACE = transarterial chemoembolization; m = month; d = day; NS = non-significant; HBV = hepatitis B virus; HCV = hepatitis C virus; PVT = portal vein invasion/thrombosis; met. = metastatic; etoh or et = alcohol-induced liver disease; 5-FU = 5-fluorouracil; LCSGJ = Liver Cancer Study Group of Japan; rx = therapy.

survival advantage in advanced HCC. It is worth noting that in four of these investigations, fewer than 20 patients constituted each study arm. More recent trials have not confirmed this benefit and are described below.

The CLIP (Cancer of the Liver Italian Program) investigators conducted a multicenter randomized study involving 477 patients with both localized and advanced HCC [55]. Over 80% of subjects were HCV infected and had either Child–Pugh Class A or B liver function. Patients received either locoregional treatment or supportive care at the discretion of treating physicians; approximately one-half of the patients underwent locoregional treatment, including surgery, ethanol injections and embolization. Patients were randomized to receive either tamoxifen 40 mg daily or no systemic therapy. Toxicities from tamoxifen occurred in 9.7% of treated patients and included thrombophlebitis, thrombocytopenia, nausea, hot flashes and pruritis; 4.7% of treated patients discontinued therapy because of side-effects. Tamoxifen therapy was not associated with survival benefit; in aggregate, median survival was 15 (tamoxifen) versus 16 months (no therapy). The lack of survival benefit was noted in both patients receiving locoregional therapy (23 versus 22 months median survival) and those not receiving additional therapy (6 versus 5 months median survival). Subset analysis did not reveal any benefit within any specific Child's or Okuda stage.

Castells *et al.* randomized 120 predominantly HCV-infected patients who were not eligible for surgical, local or embolization-based therapies to receive either tamoxifen (20 mg orally per day) versus placebo [56]. Side-effects were minimal and comparable between groups. There were no differences in survival (median approximately 6 months); no differences were apparent in subgroups based on liver dysfunction, performance status or exclusion of patients who died within 3 months of enrollment.

In a multicenter Spanish trial, Riestra *et al.* randomized 80 predominantly HCV and alcohol-induced cirrhotic patients with advanced HCC to receive tamoxifen versus placebo [57]. A majority of patients had multifocal or massive tumors and nearly one-quarter had either Okuda III liver function or portal vein invasion. More patients in the tamoxifen group had Okuda III disease than those receiving placebo. Side-effects were limited. One-year survival was 30% for those receiving tamoxifen and 38% in those receiving placebo (non-significant difference).

Recently, Chow *et al.* published results of a multicenter investigation in which 324 predominantly HBV-infected patients were randomized to receive high or intermediate doses of tamoxifen (120 and 60 mg/day, respectively) versus placebo [58]. Over 20% of patients had ECOG performance status of 2–3 and 13% had Child–Pugh class C liver dysfunction. Median survival was 2.2 and 2.1 months for the tamoxifen arms, and 2.7 months for those receiving placebo. High-dose tamoxifen was associated with diminished survival relative to placebo, and this difference remained significant after multivariate analysis was performed in order to incorporate differences in performance status and liver function between the study arms.

Liu *et al.* randomized 119 patients to receive tamoxifen or placebo [59]. Over 75% of patients were HBV infected and had either stage IV-A or IV-B (metastatic) tumor. Fourteen percent had Child–Pugh class C liver function and 22% were Okuda stage III. Survival for both arms was extremely limited (median 44 days) and there was no difference between treatment and placebo. Survival was similar when patients surviving less than month were excluded from analysis. Tamoxifen did not appear to confer survival benefit for the subset of patients whose tumors had significant estrogen or progesterone receptor expression.

Summary of trials in which tamoxifen was not associated with clinical benefit

A recent meta-analysis encompassing seven of the studies described above (689 patients) further concluded that tamoxifen confers no survival benefit versus either placebo or no therapy in advanced HCC [5]. In this analysis, the authors conclude that methodological lapses (with regards to allocation, blinding, follow-up and other factors) appear to be more prevalent in the earlier studies in which tamoxifen was associated with survival benefit. The larger, more recent studies are notable for higher overall methodological quality; these studies did not confirm any significant benefit from tamoxifen in either advanced or local HCC. It is our belief that HCC trials in which a majority of subjects die within the initial 1–2 months include patients for whom anticancer therapy is highly unlikely to be efficacious. Such trials are often an unreliable means of determining whether an investigational agent confers clinical benefit.

Tamoxifen added to chemotherapy

Two small trials conducted during the 1980s tested chemotherapy regimens with and without the addition of tamoxifen-based hormonal therapy. Melia *et al.* randomized 53 patients to receive either i.v. doxorubicin or doxorubicin plus daily tamoxifen [60]. Uchino *et al.* randomized 30 patients with unresectable HCC to receive hepatic artery doxorubicin and cisplatin, oral 5-FU and daily tamoxifen and medroxyprogesterone acetate or the same chemotherapy drugs without the hormonal agents [61]. In neither study did the addition of tamoxifen result in a significant survival advantage.

Non-tamoxifen-based hormonal therapies (Table 8)

Grimaldi *et al.* published the results of a multicenter EORTC-sponsored four-arm trial investigating the role of antiandrogen therapy in 244 patients with unresectable, untreated HCC [62]. Patients received either the antiandrogen nilutamide, the LHRH agonists goseriline or triptoreline, combined antiandrogen and LHRH agonist therapy, or placebo. A higher proportion of patients in the placebo arm had performance status of 0–1, normal albumin and HBV infection than those in the other arms. Side-effects were mild and infrequent. Median survival ranged from 2.7 to 5.8 months and was highest in the placebo arm; none of the survival differences were statistically significant.

Villa *et al.* identified a variant estrogen receptor in a portion patients with HCC [63]. The variant receptor is characterized by an exon deletion which results in an altered receptor binding domain and constitutive transcriptional activity. Tumors with variant receptors are associated with shorter doubling times, aggressive clinical behavior and have recently been demonstrated as an independent predictor of limited survival [64]. The authors detected variant receptors in approximately one-third of unresectable HCC patients presenting to their clinic (as determined by RT-PCR). They randomized 45 of these patients to receive either megestrol 160 mg/day or no therapy. Side-effects were mild and infrequent. There were no responses. Megestrol was associated with significant increase in appetite and weight-gain, and a significant survival benefit (median of 18 versus 7 months for no therapy).

Kouroumalis *et al.* (Heraklion, Crete) identified overexpression of octreotide receptors in a small percentage of patients with liver disease (including acute and chronic hepatitis, cirrhosis and HCC). They randomized 58 patients with advanced HCC to receive either octreotide, 250 μg s.c. twice daily versus no antitumor therapy. Over 50% of patients had HCV infection. Half of the patients enrolled had Child–Pugh Class C liver function and 38% were classified as Child–Pugh Class B. Over one-third of patients had tumor greater than 8 cm; a similar proportion had multifocal tumor. Octreotide was associated with disappearance of satellite tumors and disease stability. Median survival was 13 months for those receiving therapy versus 4 months for those without treatment. One-year survival also suggested a benefit from octreotide (56% for 13%). Octreotide was also associated with a weight-gain and quality-of-life benefit (54 versus 0%); the no-therapy arm did not include any placebo [65].

Yuen *et al.* at the University of Hong Kong attempted to verify these encouraging preliminary findings [66]. Their study employed long-acting octreotide (Sandostatin LAR) at a dose of 30 mg monthly and use of a placebo. Roughly half of the patients had Child–Pugh Class A and B liver dysfunction, respectively; 36% had multifocal or diffuse tumor and over one-half had portal vein invasion. A higher proportion of patients in the placebo group had diffuse tumor, portal thrombus and bilobar tumor. Side-effects were reportedly minimal. Median survival was 2 months in both treatment and placebo arm, and 1-year survival was below 20% for both arms. Octreotide was not

Table 8 Other hormonal therapy

Publication	Intervention	Survival				Liver disease	Tumor extent	Comment/misc.
		Medn	1-year	2-year	Sign			
Grimaldi *J Clin Oncol* 1998	Nilutamide 300 →150 mg p.o. qd + placebo: $n=58$	3.6 m			$p=0.19$	19% HBV included ECOG PS 3	Unresectable	
	Goseriline 3.6 mg s.c. q month (or triptoreline 3.75 mg i.m.) + placebo: $n=61$	2.7 m						
	Nilutamide + goseriline: $n=60$	3.9 m						
	Placebo + placebo: $n=59$	5.8 m						
Villa *Br J Cancer* 2000	Megestrol 160 mg p.o. qd: $n=21$	18 m			$p=0.009$	64% HBV 24% Child's C	11% PVT 47% multifocal/ diffuse	All tumors expressed *variant estrogen receptor*
	No therapy: $n=24$	7 m						
Kouroumalis *Gut* 1998	Octreotide 250 μg s.c. b.i.d.; $n=28$	13 m	56%	20%	$p<0.003$	53% HCV 24% HBV	36% >8 cm 38% multifocal	
	No therapy: $n=30$	4 m	13%	3%		38% Child's B 50% Child's C		
Yuen *Hepatology* 2002	Octreotide LAR 30 mg i.m. q month (initial octreotide 250 μg s.c. b.i.d. × 14 d): $n=35$	2 m			NS	43% Child's A 51% Child's B	36% multifocal/ diffuse 54% PVT 17% met	
	Placebo: $n=35$	2 m						

m = month; NS = non-significant; HBV = hepatitis B virus; HCV = hepatitis C virus; PVT = portal vein invasion/thrombosis; met. = metastatic; etoh = alcohol-induced liver disease; LAR = long-acting.

associated with improvement in performance status. It is worth noting that survival in the placebo arm in the Hong Kong study was lower than that seen in the no-therapy group for the Greek study, despite a similar proportion of multifocal tumor in both studies, and despite a significantly higher percentage of patients with Child–Pugh class A liver dysfunction in the Hong Kong group. The disparate findings of the trials reported by Yuen and Kouroumalis suggest that octreotide remains an investigational modality in advanced HCC; additional study is warranted.

Conclusions regarding systemic therapy in unresectable HCC

(i) Cytotoxic chemotherapy may confer modest survival benefit in advanced HCC, although this benefit does not extend to patients with severe hepatic dysfunction or tumor advanced such that expected survival is less than 3 months.

(ii) Chemotherapeutic agents which have demonstrated potential for efficacy include doxorubicin, cisplatin and oral fluoropyrimidines.

(iii) Although doxorubicin is considered a standard therapy by some investigators, there exists only a single trial in which this agent was compared to supportive therapy; toxicities in this trial were unacceptably high and median survival for all groups was less than 3 months.

(iv) Optimal means of chemotherapeutic delivery in locally advanced HCC is uncertain. Infusion via the hepatic artery appears to confer less toxicity than i.v. administration. However, potential for complications related to implanted arterial catheters is significant.

(v) The use of ongoing systemic chemotherapy following TACE (chemoembolization) was not shown to confer benefit in two small randomized trials.

(vi) IFN-based immunotherapies may confer some survival benefit in advanced HCC; however, the doses required have been associated with toxicity which precludes widespread non-investigational use. Addition of low-dose IFN-α to cytotoxic chemotherapy (hepatic artery cisplatin) conferred a survival benefit in a single, small trial and may represent a low-toxicity means of enhancing survival.

(vii) IFN-α has been associated with diminished incidence of primary HCC when investigated in cirrhotic populations. There has been some association of IFN-α with secondary prevention following surgical resection. This benefit may also be significant following embolization in unresectable HCC patients with limited-stage disease and warrants further investigation.

(viii) ^{131}I therapy, given via the hepatic artery, appears safe in unresectable, locally advanced HCC. Initial trials suggest potential for survival benefit; further investigations with [^{131}I]lipiodol will be essential.

(ix) Tamoxifen, either at low or high doses, does not confer survival benefit for early or late stage HCC.

(x) Identification of variant estrogen receptors represents an initial attempt at molecular characterization enabling more tailored hormonal therapy. The positive report by Villa *et al.* utilizing megestrol in patients whose tumors display these variant receptors are encouraging. Larger studies will hopefully confirm this benefit.

(xi) The divergent results of two studies investigating octreotide prevent definitive conclusion. Although the limited toxicity observed makes octreotide an attractive option in advanced HCC, its cost is prohibitive without definitive confirmation of benefit. Octreotide remains an investigational agent in HCC.

(xii) The potential of an HMG-CoA reductase inhibitor (pravastatin) to prolong survival at limited cost and toxicity is appealing. Additional studies will hopefully confirm or clarify the extent of survival benefit.

Future directions

Hepatocellular carcinoma is a major disease worldwide. Therapy remains difficult in many clinical situations, often because of advanced tumor at presentation and concomitant cirrhosis and hepatic dysfunction. Although the mainstay of curative therapy remains surgical, an increasing number of medical interventions have demonstrated potential to prolong survival. Transarterial embolization has been more clearly associated with meaningful benefit in recent, well-conducted randomized trials and meta-analyses.

Despite widespread nihilism, non-embolization-based therapies may confer survival benefit in unresectable HCC. As with many other adult solid tumors in which therapy has evolved during the past decade (i.e. colorectal and breast cancer), advances are likely to be incremental and no one agent or trial is likely to result in an astounding improvement in prognosis or survival.

Several trials have demonstrated [^{131}I]lipiodol to be safe and potentially efficacious, even in locally advanced tumor. This agent is not available in many parts of the world; however, ongoing investigations with other infusional radiotherapies will hopefully provide clinicians with meaningful alternatives in the coming years [67]. Chemotherapy agents, including oral 5-FU derivatives, and i.v. and arterial doxorubicin and cisplatin, have demonstrated modest potential for benefit in advanced

HCC. More rigorous study will hopefully clarify the role of these drugs, especially in combination with more novel therapies.

As more is elucidated regarding the biology of HCC, additional agents appear promising for therapy. Because HCC is a highly vascular tumor in which vascular recruitment and invasion contribute significantly to pathogenesis, we have commenced a study with the anti-VEGF agent bevacizumab in unresectable HCC [68]. Other biologic agents, including those that inhibit EGF receptor and cell signaling pathways, will hopefully contribute to improved therapeutic options for patients with both limited and advanced stages of this illness.

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