Conventional oral systemic chemotherapy for postoperative hepatocellular carcinoma: A systematic review

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Abstract. The findings of randomized clinical trials (RCTs) regarding the efficacy of adjuvant conventional oral systemic chemotherapy (COSC) for patients with hepatocellular carcinoma (HCC) following curative hepatic resection (HR) are contradictory. Therefore, a systematic review of RCTs is required to evaluate the clinical efficacy of adjuvant COSC. Sources such as Medline, Embase and the Cochrane Library were systematically searched and all the RCTs comparing curative HR alone to HR plus COSC for HCC were identified. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. No treatment-related mortality was reported by the included RCTs and the adverse effects of COSC were generally mild. However, adjuvant COSC did not achieve a statistically significant improvement in the 1-, 3- and 5-year overall survival (OR=1.43, 95% CI: 0.58-3.56, P=0.44; OR=1.39, 95% CI: 0.75-2.55, P=0.29; and OR=1.20, 95% CI: 0.46-3.16, P=0.71, respectively). In addition, adjuvant COSC did not achieve a statistically significant decrease in the incidence of 1-, 3- and 5-year tumor recurrence, with pooled ORs of 0.92 (95% CI: 0.26-1.35, P=0.66); 0.82 (95% CI: 0.66-1.01, P=0.06); and 0.84 (95% CI: 0.71-1.01, P=0.06), respectively. Narrative reviews offer no evidence supporting the use of COSC. Adjuvant COSC has provided marginal benefits for HCC patients following curative HR. Considering the efficacy of sorafenib for advanced HCC and the results of this systematic review, no further trials should be performed to assess the efficacy of adjuvant COSC.

Introduction

Hepatocellular carcinoma (HCC) is a malignancy associated with a poor prognosis and has a heterogeneous composition, with multiple variables that vary among different regions. Although several novel treatment options have been investigated and used in the clinical setting, hepatic resection (HR) remains the primary treatment for HCC. However, even after curative resection, recurrence is common and remains the main cause of mortality. The 3-year tumor recurrence rate was reported to be >60% following HR (1,2) and the 5-year overall survival (OS) rate ranges between 39 and 50% (3,4). Consequently, adequate and effective adjuvant therapy is essential to improve the OS of HCC patients.

Various types of postoperative therapies, such as transarterial therapy with or without embolization, systematic therapy, interferon, lamivudine, vitamin A and K2 analog and adoptive immunotherapy, have been reported for HCC patients following curative treatment. However, interferon is frequently associated with various adverse effects (5) and postoperative transarterial chemoembolization appears to be promising only for HCC patients with a high risk of recurrence (6). Adoptive immunotherapy, although associated with a lower recurrence rate following surgery for HCC, does not appear to increase OS (7), whereas the manufacturing operation and therapeutic process are complex. The number of randomized clinical trials (RCTs) investigating the effect of adjuvant vitamin A or K2 analog and lamivudine therapy is limited. Orally administered chemotherapy is a type of systemic treatment. As a convenient and non-invasive therapy, oral chemotherapeutic drug administration is easily adopted.

Although conventional systemic chemotherapy is well tolerated by inoperable HCC patients (8,9), HCC is widely considered to be chemotherapy-resistant, as the response rates are ~20% for single-agent as well as combination chemotherapy (10). One of the most widely used chemotherapeutic agents is 5-fluorouracil. Several investigators have attempted to improve the survival of HCC patients postoperatively by conventional oral systemic chemotherapy (COSC) over the last few decades. However, these trials reported contradictory findings. Therefore, a systematic review is required to provide a more comprehensive analysis and assess the efficacy of COSC.

Materials and methods

Identification of trials. The Medline, Embase and Cochrane Library electronic databases were systematically searched through to April, 2012 and comparative studies investigating

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curative HR with and without COSC were identified using any of the following key words: hepatocellular carcinoma, hepatic tumor, liver tumor, postoperative, adjuvant, chemotherapy, or oral. The search was not limited to controlled or randomized trials for minimizing the chances of missing a study. Manual search of relevant references and review articles was also performed. There were no date and language restrictions. Only RCTs were included.

RCTs which assessed the effect of COSC for postoperative HCC were included in this review. Studies investigating liver metastases or postoperative recurrent HCC were excluded. The patients in the control group only received curative HR. The studies identified during the search were screened independently by two reviewers. Any disagreements were arbitrated by a third reviewer.

Types of outcome measures. The primary outcomes evaluated in this review were OS and recurrence rates. The secondary outcome was incidence of adverse events attributable to COSC.

Quality assessment. Two reviewers independently evaluated the quality of each retrieved trial in terms of randomization by sequence generation, allocation concealment, blinding of outcome assessors and reporting of intention-to-treat analysis. The trials were considered to be of low quality if they reported none of the items, of moderate quality if they reported on one or two items and of good quality if they reported on three or four items. The reporting of this systematic review is in accordance with the QUOROM statement (11).

Data extraction. Two reviewers independently extracted data regarding author details, methodological quality, number of patients, patient characteristics, interventions and outcomes. Discrepancies were resolved by consensus. When multiple publications of the same trial were identified, data were extracted from the multiple publications and reported as a single trial.

Statistical analysis. The data from each study were analyzed using the RevMan 5.1 software package. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for OS and recurrence rate outcomes. Fixed- and random-effects models were applied in an 'intention-to-treat' analysis, i.e., all the patients were evaluated according to their group allocation. Patients whose endpoint was unknown were considered to be deceased or to have suffered tumor recurrence. Homogeneity between trials was analyzed using the χ^2 test, with significance set at $P>0.1$; the extent of heterogeneity was assessed by calculating I^2. The point estimate of the OR was considered statistically significant at $P<0.05$ if the 95% CI did not include the value 1.

Results

Identification and characteristics of selected studies. From 916 citations identified by database searches, three eligible RCTs (12-14) involving a total of 286 patients were included in this systematic review (Fig. 1). One study was conducted in China (12) and two in Japan (13,14). A definitive diagnosis of HCC was made based on histological evidence or a combina-
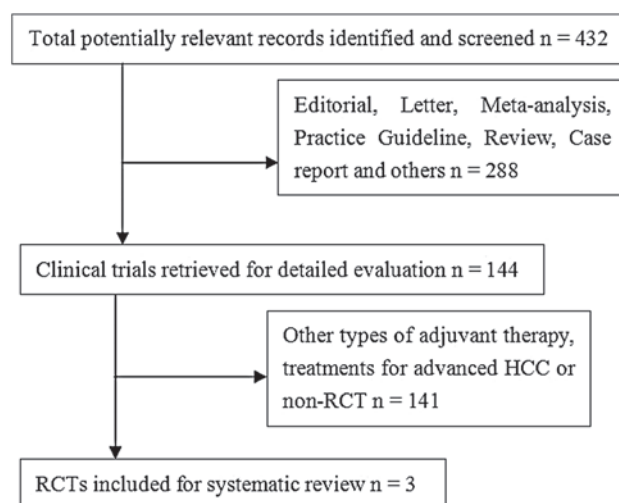

Figure 1. Flow chart of the study selection process. HCC, hepatocellular carcinoma; RCT, randomized clinical trial.

tion of several imaging modalities, e.g., hepatic angiography, enhanced computed tomography and magnetic resonance imaging. All the HCC patients underwent curative HR. No patient in the control group received any type of chemopreventive therapy prior to the discovery of recurrent HCC. The median follow-up was >4 years in all three RCTs (12-14). The patients in the treated group received oral capecitabine (12), uracil-tegafur (13), or carmofur (14), which are fluoropyrimidine drugs. Across the three studies, recurrence was measured and assessed in the same way by at least two imaging methods. The characteristics of the studies included in the review are summarized in Table I. In order to compare the efficacy of adjuvant COSC of other studies to the included studies, three other studies were systematically reviewed, including two RCTs (15,16) and one case-control trial (17). All the HCC patients in these three trials underwent curative HR (15-17). The patients in the control group of two trials only received supportive care following HR (15,17). By contrast, the patients in the treated group received adjuvant COSC, with or without other types of chemotherapy.

Quality of included RCTs. The risks of bias in the studies included in this systematic review are detailed in Table II. The methodological quality was considered to be high in the first (12), moderate in the second (13) and low in the third study (14).

Efficacy. Some of the efficacy of the included RCTs (12-14) and other trials (15-17) of adjuvant COSC for HCC patients are summarized in Table III.

OS. All the RCTs (12-14) described the OS. In the study by Xia *et al* (12), the median OS time was longer in the capecitabine group (60.0 vs. 52.5 months), but the difference was not statistically significant (P=0.22). The study by Yamamoto *et al* (14) concluded that the OS of patients with stage I disease was higher in the oral carmofur compared to that in the control group (P=0.08). However, in patients with stage II disease, no significant difference was observed (P=0.77). Interestingly, Hasegawa *et al* (13) drew an opposite conclusion, reporting

Table I. Baseline characteristics of randomized clinical trials included into the systematic review.

Study	Mean follow-up, years (range)	Child-Pugh classification (A/B)	Sample size (n)	Tumor size (median, cm)	Hepatitis (n) (HBV/HCV)	Cirrhosis (%)	Vascular invasion (n)	(Refs.)
Xia et al	4.0 (0.3-5.4)	60/0	T:30	7.27	26/NR	63.3	12	(12)
			C:30	6.34	24/NR	70.0	10	
Hasegawa et al	4.8 (0.5-7.9)	138/21	T:79	3.3	14/58	53.2	18	(13)
			C:80	3.4	15/56	47.5	17	
Yamamoto et al	4-6	NR	T:35	NR	NR	100.0	NR	(14)
			C:32	NR	NR	100.0	NR	

HBV, hepatitis B virus; HCV, hepatitis C virus; T, treated group; C, control group; NR, not reported.

Table II. Methodological quality assessment and internal validity of the included randomized clinical trials.

Study	Random allocation	Concealment of random allocation	Blinding of persons who assess treatment effects	Intention-to-treat analysis	(Refs.)
Xia et al	+	+	-	+	(12)
Hasegawa et al	+	-	-	+	(13)
Yamamoto et al	-	-	-	-	(14)

Table III. Results of randomized clinical trials and other clinical trials of adjuvant conventional oral systemic chemotherapy for hepatocellular carcinoma.

Study	Drugs and dose of the treated and control groups	Outcomes	Treated group (%)	Control group (%)	P-value	(Refs.)
Xia et al	Two weeks of capecitabine (1,000 mg/m^2) twice a day, followed by 1 week of rest, for 4-6 cycles	5-year DFS	46.7	23.3	<0.05	(12)
	Supportive care	5-year OS	62.5	39.8	>0.05	
Hasegawa et al	Oral uracil-tegafur (300 mg/day) for 1 year	5-year DFS	29	29	>0.05	(13)
	Supportive care	5-year OS	58	73	>0.05	
Yamamoto et al	Oral carmofur (200 mg) twice daily for as long as possible	5-year DFS[a]	50	19	<0.05	(14)
	Supportive care	5-year OS[a]	72	49	<0.05	
Kohno et al	Oral uracil-tegafur (300 mg/day) for 1 year, plus transarterial chemotherapy once (epirubicin 40 mg/m^2)	5-year DFS	17	14	>0.05	(16)
	Oral uracil-tegafur (300 mg/day) for 1 year	5-year OS	35	30	>0.05	
Ono et al	Transarterial chemotherapy (epirubicin 40 mg/m^2); then intravenous chemotherapy (epirubicin 40 mg/m^2), once every 3 months for 2 years; in addition, oral carmofur (300 mg/day) for 2 years	5-year DFS	32	22.5	>0.05	(15)
	Supportive care	5-year OS	31.5	57	>0.05	
Takenaka et al	Oral uracil-tegafur or carmofur (300-400 mg/day) for 18 months	3-year DFS	50	15	>0.05	(17)
	Supportive care					

[a]Patients with stage I disease. DFS, disease-free survival; OS, overall survival.

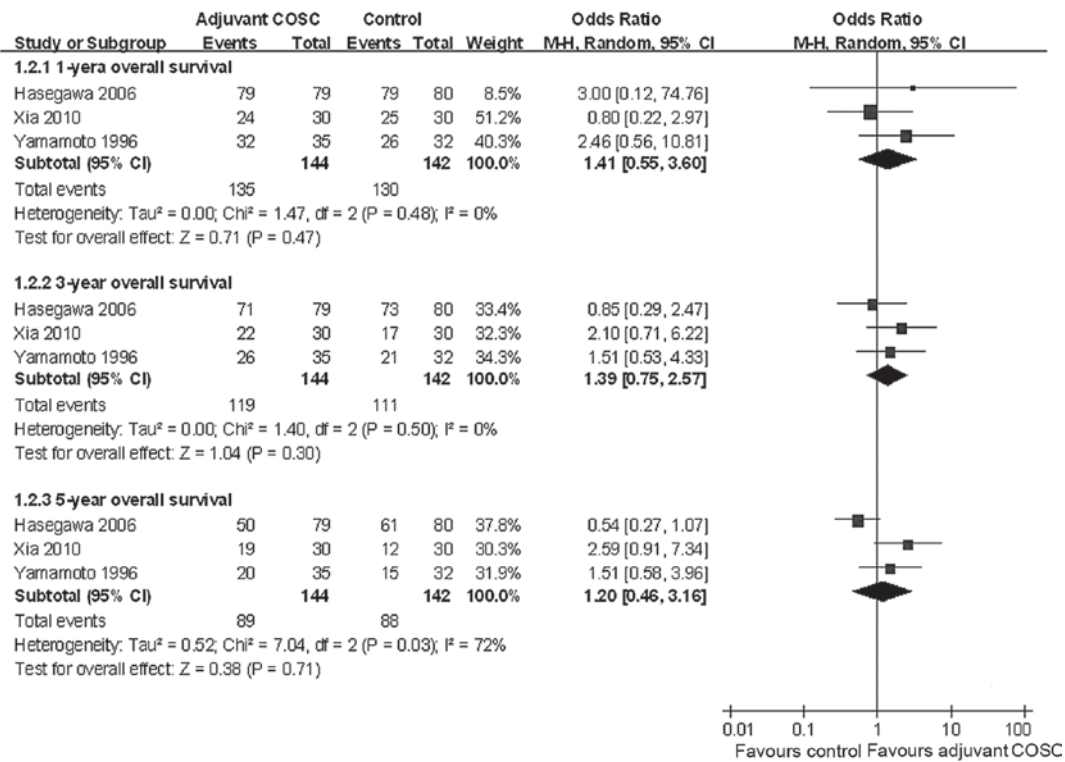| Study or Subgroup	Adjuvant COSC Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 1-yera overall survival						
Hasegawa 2006	79	79	79	80	8.5%	3.00 [0.12, 74.76]
Xia 2010	24	30	25	30	51.2%	0.80 [0.22, 2.97]
Yamamoto 1996	32	35	26	32	40.3%	2.46 [0.56, 10.81]
Subtotal (95% CI)		**144**		**142**	**100.0%**	**1.41 [0.55, 3.60]**
Total events	135		130			
Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.47)						
1.2.2 3-year overall survival						
Hasegawa 2006	71	79	73	80	33.4%	0.85 [0.29, 2.47]
Xia 2010	22	30	17	30	32.3%	2.10 [0.71, 6.22]
Yamamoto 1996	26	35	21	32	34.3%	1.51 [0.53, 4.33]
Subtotal (95% CI)		**144**		**142**	**100.0%**	**1.39 [0.75, 2.57]**
Total events	119		111			
Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.2.3 5-year overall survival						
Hasegawa 2006	50	79	61	80	37.8%	0.54 [0.27, 1.07]
Xia 2010	19	30	12	30	30.3%	2.59 [0.91, 7.34]
Yamamoto 1996	20	35	15	32	31.9%	1.51 [0.58, 3.96]
Subtotal (95% CI)		**144**		**142**	**100.0%**	**1.20 [0.46, 3.16]**
Total events	89		88			
Heterogeneity: Tau² = 0.52; Chi² = 7.04, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 0.38 (P = 0.71)						

Figure 2. Meta-analysis of hepatocellular carcinoma patients' overall survival in randomized trials comparing hepatic resection plus conventional oral systemic chemotherapy (COSC) to hepatic resection alone. CI, confidence interval.

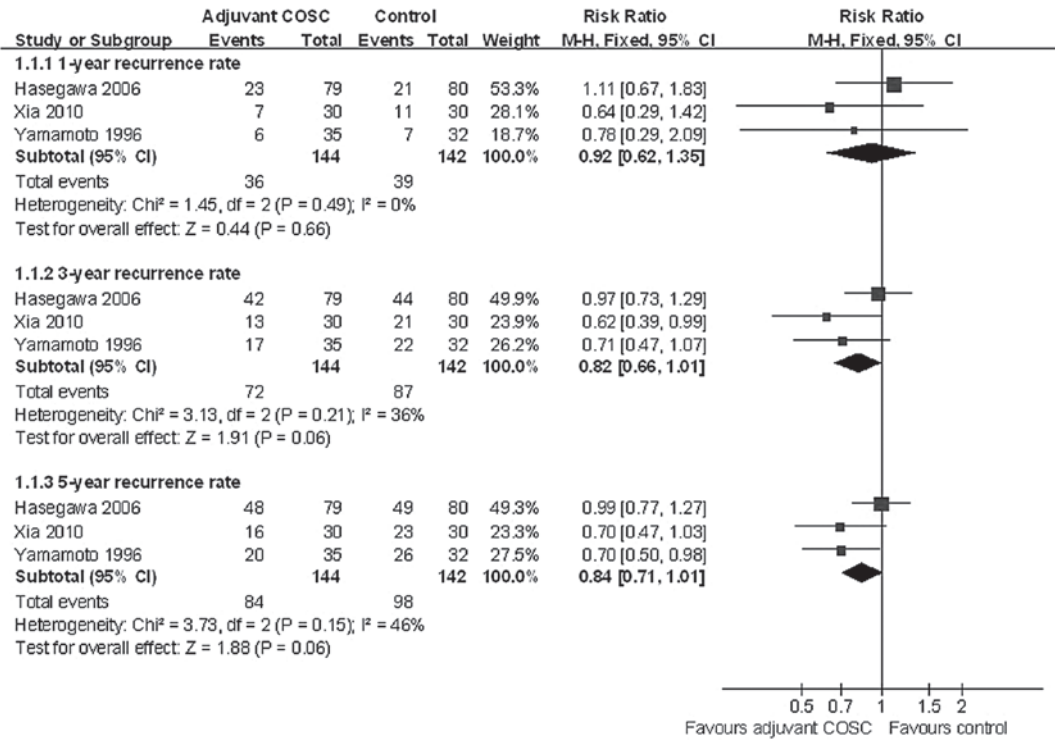| Study or Subgroup	Adjuvant COSC Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 1-year recurrence rate						
Hasegawa 2006	23	79	21	80	53.3%	1.11 [0.67, 1.83]
Xia 2010	7	30	11	30	28.1%	0.64 [0.29, 1.42]
Yamamoto 1996	6	35	7	32	18.7%	0.78 [0.29, 2.09]
Subtotal (95% CI)		**144**		**142**	**100.0%**	**0.92 [0.62, 1.35]**
Total events	36		39			
Heterogeneity: Chi² = 1.45, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.1.2 3-year recurrence rate						
Hasegawa 2006	42	79	44	80	49.9%	0.97 [0.73, 1.29]
Xia 2010	13	30	21	30	23.9%	0.62 [0.39, 0.99]
Yamamoto 1996	17	35	22	32	26.2%	0.71 [0.47, 1.07]
Subtotal (95% CI)		**144**		**142**	**100.0%**	**0.82 [0.66, 1.01]**
Total events	72		87			
Heterogeneity: Chi² = 3.13, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.1.3 5-year recurrence rate						
Hasegawa 2006	48	79	49	80	49.3%	0.99 [0.77, 1.27]
Xia 2010	16	30	23	30	23.3%	0.70 [0.47, 1.03]
Yamamoto 1996	20	35	26	32	27.5%	0.70 [0.50, 0.98]
Subtotal (95% CI)		**144**		**142**	**100.0%**	**0.84 [0.71, 1.01]**
Total events	84		98			
Heterogeneity: Chi² = 3.73, df = 2 (P = 0.15); I² = 46%						
Test for overall effect: Z = 1.88 (P = 0.06)						

Figure 3. Meta-analysis of hepatocellular carcinoma recurrence in randomized trials comparing hepatic resection plus conventional oral systemic chemotherapy (COSC) to hepatic resection alone. CI, confidence interval.

that OS was marginally but not significantly worse in the uracil-tegafur compared to that in the control group (P=0.08).

A meta-analysis revealed that adjuvant COSC did not significantly increase the 1-, 3- and 5-year OS, with pooled ORs of 1.43 (95% CI: 0.58-3.56, P=0.44), 1.39 (95% CI: 0.75-2.55, P=0.29) and 1.20 (95% CI: 0.46-3.16, P=0.71), respectively (Fig. 2).

There were no significant differences between the two groups regarding long-term survival in the study by

Kohno *et al* (16) (P=0.22) and the study by Ono *et al* (15) (P=0.14).

Recurrence rates. All the three RCTs (12-14) reported recurrence rates. Compared to supportive care, capecitabine significantly decreased the recurrence rate (P=0.046) (12). Carmofur also improved the recurrence-free survival rates of patients with stage I disease (P=0.04). However, in patients with stage II disease, no significant difference was observed (P=1.00) (14). Yamamoto *et al* (14) concluded that the potential benefits of carmofur on tumor recurrence must be weighed against the risks of adverse reactions in patients with mild liver dysfunction. In the third study, however, the recurrence-free survival curves were similar between the groups (P=0.87) (13).

Although adjuvant COSC was expected to reduced recurrence, a meta-analysis did not revealed a statistically significant decrease in the incidence of the 1-, 3- and 5-year HCC recurrence rate, with pooled ORs of 0.92 (95% CI: 0.62-1.35, P=0.66); 0.82 (95% CI: 0.66-1.01, P=0.06); and 0.84 (95% CI: 0.71-1.01, P=0.06), respectively (Fig. 3).

All the three trials demonstrated no statistically significant difference in the disease-free survival (DFS) curves between the control and COSC with or without other type of chemotherapy groups (15-17).

Adverse effects of adjuvant COSC. There was no reported treatment-related mortality. In the study by Xia *et al* (12), the observed adverse reactions were generally mild. Nausea (23.3%) and diarrhea (16.7%) were the most common adverse effects associated with oral capecitabine. Two patients (7%) withdrew from capecitabine therapy due to repeated grade III nausea or low white blood cell and platelet counts. Although treatment with uracil-tegafur was temporarily or permanently discontinued in 41% of the patients due to adverse effects, liver toxicity was negligible. Moreover, all the adverse events responded to conservative therapy (13). However, carmofur administration was suspended due to side effects in 9 of 21 patients (42.9%) with clinical stage I and in 3 of 6 patients (50%) with stage II cirrhosis, although the symptoms resolved within 2 months of suspension of the drug. The most common adverse effects were neuropathy (18.5%) and liver dysfunction (18.5%) (14).

Discussion

The aim of this systematic review was to assess the available evidence regarding the effect of HR plus COSC on OS and tumor recurrence in HCC patients. On the whole, adjuvant COSC with capecitabine, uracil-tegafur, or carmofur was well tolerated by the majority of the HCC patients. Two included RCTs indicated that adjuvant COSC significantly decreased the recurrence rate of HCC patients following curative HR (12,14). However, the meta-analysis demonstrated that there was no statistically significant benefit regarding OS and tumor recurrence. Moreover, another two RCTs which investigated the efficacy of adjuvant COSC plus transarterial chemotherapy (15,16) and one case-control trial (17) did not demonstrate a statistically significant benefit of adjuvant COSC. These results were consistent with those of former studies evaluating the efficacy of COSC (9,18) and systemic intravenous chemotherapy for advanced HCC (19-22).

Conventional systemic therapy with a single agent or a combination of agents has provided marginal survival benefits.

Theoretically, adjuvant COSC may prevent metastatic recurrence caused by HCC cells present in the microcirculation, which were not identified by preoperative imaging, with fewer severe side effects on the liver. It is hypothesized that tumoricidal effects on lesions in the precancerous stage may be achieved by oral intake of anticancer agents, which induces a high portal drug concentration (14). Indeed, systemic chemotherapy is often difficult to perform on cirrhotic HCC patients following HR. First, the majority of the HCC patients are cirrhotic. Anticancer drugs may lead to further impairement of liver function. Hence, cirrhosis exerts a significant effect on the pharmacokinetics of systemic therapy for HCC. Second, certain drug resistance genes of HCC cells, such as P-glycoprotein, glutathione-S-transferase, heat shock proteins and mutations in p53, are overexpressed. Unlike other cancers, the majority of the reported deaths in HCC patients are attributed to liver disease rather than to HCC (13). In cirrhotic patients, adjuvant chemotherapy is associated with worse DFS and OS by negatively affecting liver function (14,23). Furthermore, accelerated repopulation of surviving tumor cells may occur after sequential chemotherapy (24). A marginally higher incidence of advanced recurrence in the adjuvant COSC group was reported by Hasegawa *et al* (13) and Lai *et al* (25) reported that adjuvant chemotherapy was associated with more frequent extrahepatic recurrences and a worse outcome. Therefore, systemic chemotherapy is not widely used. The majority of the HCC patients in this systematic review were infected by hepatitis B/C virus and/or cirrhotic. The meta-analysis demonstrated that adjuvant COSC was likely to decrease the recurrence rate and improve the OS. However, no statistically significant benefit was observed.

Certain double-blind, multicenter, phase III RCTs indicated that oral sorafenib is effective for the treatment of advanced HCC (26-28). A phase III trial is ongoing to evaluate the safety and efficacy of adjuvant sorafenib compared to placebo in the treatment of HCC. Oral sorafenib may prove to be a viable option for the treatment of HCC following curative HR.

A major drawback of this review is that the number of the included patients, who were all Asian, was relatively small. Although we systematically searched Medline, Embase and the Cochrane Library databases and reviewed two RCTs and one case-control trial investigating adjuvant systemic chemotherapy for HCC, there is a risk of random errors. Furthermore, some of the important patient characteristics, such as tumor size and hepatitis status, were not described. In addition, the randomization procedure and allocation concealment remained unclear in certain studies. Due to these limitations, the results and the conclusions of the present study should be interpreted with caution.

In summary, although adjuvant COSC appears to be well tolerated, our results demonstrated only marginal benefits for HCC patients undergoing curative HR. Further trials should be conducted to investigate novel adjuvant therapies, such as treatment with multikinase inhibitors.

Acknowledgements

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