Chinese Herbal Medicine and Chemotherapy in the Treatment of Hepatocellular Carcinoma: A Meta-analysis of Randomized Controlled Trials

Xiaojuan Shu, MPH (candidate), Michael McCulloch, LAc, MPH, Hang Xiao, MPH, PhD, Michael Broffman, LAc, and Jin Gao, MD, PhD

Background: **Hepatocellular carcinoma (HCC), one of the most common malignancies worldwide, is highly resistant to standard therapy. It is unclear whether chemotherapy, arterial embolization, or arterial chemoembolization improve survival advantage enough to justify their high toxicity. Treatment with Chinese herbal medicine has been explored, combining herbs that stimulate host immune response with those that have cytotoxic activity against HCC cells. The authors sought to evaluate the effectiveness of Chinese herbal medicine combined with chemotherapy. The hypothesis was that Chinese herbal medicine added to chemotherapy for the treatment of HCC would improve survival and tumor response, when compared to treatment with chemotherapy alone.** ***Methods:*** **The authors searched the databases TCMLARS, PubMed, and EMBASE as well as the bibliographies of studies identified in the systematic search for potentially relevant titles or abstracts of studies in any language. They retained those that (1) treated only HCC patients, (2) were described as randomized or reported that there was no statistical difference between treatment groups, (3) gave patients either Chinese herbal medicine therapy combined with chemotherapy in the treatment group or chemotherapy alone in the control group, and (4) provided data on the number of enrolled subjects and responders and nonresponders for tumor response and survival. The authors used random effects meta-analysis to combine data.** ***Results:*** **Twenty-six studies representing 2079 patients met the inclusion criteria. Chinese herbal medicine combined with chemotherapy, compared to chemotherapy alone, improved survival at 12 months (relative risk [RR], 1.55; 95% confidence interval [CI], 1.39-1.72; $P < .000$), 24 months (RR, 2.15; 95% CI, 1.75-2.64; $P < .000$), and 36 months (RR, 2.76; 95% CI, 1.95-3.91; $P < .000$). Tumor response increased (RR, 1.39; 95% CI, 1.24-1.56; $P < .000$).** ***Conclusions:*** **These findings provide promising evidence that combining Chinese herbal medicine with chemotherapy may benefit patients with HCC. Because of the low quality of these studies, these findings should be confirmed through conducting high-quality, rigorously controlled trials.**

Keywords: ***hepatocellular carcinoma (HCC); chemotherapy; Chinese herbal medicine; randomized, controlled trials (RCTs); quasi-randomized, controlled trials (quasi-RCTs); survival; tumor response (TR)***

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer worldwide, with increasing incidence.[1] The incidence ranges from 1 to 4 cases per 100 000 population in Western Europe and North America to 50 to 150 cases per 100 000 population in parts of Asia and Africa, where HCC is responsible for a large proportion of cancer deaths.[2] Its treatment remains a controversial issue, despite the progress that has been made during the past decades, as most HCC patients are diagnosed at late stages and receive only palliative treatments not intended to extend survival.[1] Untreated patients with advanced disease have a 1-year survival rate of 29%, a 2-year survival rate of 16%, and a 3-year survival rate of 8%.[3]

Arterial embolization, chemoembolization, and arterial chemotherapy are the major procedures in chemotherapy. Arterial embolization or chemoembolization is a technique combining intra-arterial chemotherapy and selective ischemia and was developed as an alternative to conventional systemic or intra-arterial chemotherapy. It is intended to induce tumor necrosis through administration of chemotherapy and an embolizing agent directly into the tumor by way of the feeding artery. The cytotoxic effect of arterial occlusion can be potentiated by labeling the infusion with radioactive isotopes or by adding cytotoxic drugs. Arterial embolization or chemoembolization includes

XS, MM, and MB are at the Pine Street Foundation, San Anselmo, California. MM and JG are at the Institute of Biophysics, Chinese Academy of Sciences, Beijing P.R. China. XS and HX are in the School of Public Health, Nanjing Medical University, Nanjing, P.R. China.

Correspondence: Michael McCulloch, LAc, MPH, Pine Street Foundation, 124 Pine Street, San Anselmo, CA 94960. E-mail: mcculloch@pinestreetfoundation.org.

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procedures such as transcatheter arterial chemoembolization, transarterial embolization, hepatic arterial chemoembolization, and hepatic arterial embolization. Arterial chemotherapy is not aimed to achieve arterial occlusion. It includes procedures such as transarterial infusion, hepatic arterial infusion, and intravenous chemotherapy. However, these procedures are associated with their own potentially life-threatening toxicities and complications, such as severe postembolization syndrome, hepatic insufficiency, abscess, or infarction.[4] In addition, they have shown only slightly improved survival or no survival advantages in previous studies.[5-7] Meta-analysis of randomized controlled trials of treatment with chemoembolization or embolization has shown only a modest advantage in 2-year survival for patients with unresectable HCC, compared with conservative management.[8] The same meta-analysis revealed that tamoxifen provided no advantage in 1-year survival.[8] Since the prognosis with existing therapy is so poor, we sought to evaluate the clinical evidence for effectiveness of Chinese herbal medicine in combination with systemic chemotherapy for the treatment of HCC.

In China, herbal medicine is frequently combined with chemotherapy in the treatment of liver cancer, usually in formulas that combine various Chinese herbs into one treatment strategy. In this meta-analysis, we sought to assess the effectiveness of this therapy for HCC by analyzing data from studies that compared treatment with Chinese herbal medicine combined with chemotherapy to treatment with chemotherapy alone.

Methods

Systematic Search

Retrieval of studies in all languages was performed through systematic searching of the databases TCMLARS (1984-August 2004; www.cintcm.com), PubMed (1966-August 2004; www.pubmed.gov), and EMBASE (1974-August 2004; www.embase.com) using the keywords *liver cancer*, *chemotherapy*, *Chinese medicine*, and *randomized controlled trials*. We also searched the bibliographies of review papers and published randomized controlled trials identified in our systematic search.

Criteria for Inclusion

To be included in this meta-analysis, a study had to fulfill the following criteria: (1) only patients with HCC were included, (2) studies were described as randomized or had the design elements of quasi-randomized studies (studies did not mention adoption of randomization but reported there was no statistical difference between 2 groups), (3) HCC patients were given either Chinese herbal medicine therapy in combination with chemotherapy in the treatment group or chemotherapy alone in the control group, and (4) authors provided necessary data on the number of responders and nonresponders for the end points of tumor response and survival sufficient to calculate relative risks (RRs) and 95% confidence intervals (CIs).

Criteria for Exclusion

Randomized controlled trials were excluded if they (1) were not described as randomized or quasi-randomized, (2) did not provide information concerning survival or tumor response, (3) included patients with cholangiocellular carcinomas or liver metastases of primary cancers other than liver, (4) did not contain an experimental arm treated with Chinese medicine combined with chemotherapy and control arm treated with chemotherapy alone, or (5) were duplicate publications of other studies previously identified in our systematic search. Decisions on whether to include or exclude trials and how to group studies for analysis by end points reported were made before conducting the meta-analysis.

Criteria for Combinability

Since there is no successful standard treatment for HCC, there are few published trials using exactly the same chemotherapy treatments and same Chinese herbal formula. As has been done in previous meta-analyses of chemotherapy for HCC, we combined studies in which patients in the treatment group were treated with the new therapy being evaluated and those in the control group were treated with standard chemotherapy alone.[7-9] We also sought to separately meta-analyze any subgroups of studies that all used the same herbal combination.

Data Collection and Abstraction

Two reviewers (X.S. and M.M.) independently reviewed the retained studies. Since prior work has shown that blinding during study selection and data extraction does not result in either a clinically or a statistically significant effect on the summary effect measure of a meta-analysis,[10] we chose a nonblinded design for data extraction.

Analysis of Outcomes

The primary outcome of interest was the proportion of patients surviving at 6, 12, 24, and 36 months. The secondary outcome of interest was tumor response.

Survival. We calculated survival using the proportion of subjects surviving among the total number of

subjects, separately for each treatment group. The ratio for improvement in survival at each time point was calculated as the proportion of subjects alive in the Chinese herbal medicine combined with chemotherapy group divided by the proportion of subjects alive in the chemotherapy-only group.

Objective tumor response. We selected studies that reported tumor response using the World Health Organization scale.[11] Following a method used in a previous meta-analysis of studies treating HCC patients with chemotherapy,[12] we calculated tumor response as any response (complete response plus partial response) divided by the total (complete response plus partial response plus no change plus progressive disease), separately for each treatment group. The RR of tumor response was calculated as the probability of any tumor response in the herbal medicine combined with chemotherapy group divided by the probability of any tumor response in the chemotherapy-only group.

Pooled analysis. We used the Stata statistical software package (version 8.0; Stata Corp, College Station, Tex) for data management and analysis. All analyses were performed on an intention-to-treat basis. We used the random effects method to calculate pooled treatment effects.[13] An RR value greater than 1.0 was considered to be consistent with a beneficial effect of Chinese herbal medicine combined with chemotherapy (vs chemotherapy alone) in the treatment of patients with HCC.

Qualitative Analysis

Study quality. To evaluate study quality, we used the Jadad scale, a validated 5-point scale developed to evaluate the quality of reporting in studies included in a meta-analysis.[14,15] The scale assigns a score of 0 or 1 for each of the following quality criteria, whether (1) the study was described as randomized, (2) the authors reported the method of randomization, (3) the use of blinding was reported, (4) the method for concealment of allocation was reported, and (5) authors accounted for withdrawals and dropouts. Thus, a highest-quality study would receive a score of 5 and a lowest-quality study a score of 0.

Results

Selection of Trials

After an initial screening of titles and abstracts, 385 potentially relevant clinical trials of HCC were identified. We then performed a second screening of these 385 studies and retained 126 published full papers, which were randomized controlled trials assessing Chinese herbal medicine in the treatment of HCC. After further evaluation, we excluded 9 studies because of nonrandomization, 13 studies because they lacked relevant end points, 24 studies because other cancers were included, 51 studies because they were missing either a qualified experimental group or controlled group, and 3 studies because they were duplicate publications of other studies previously identified in our systematic search. This yielded a total of 24 randomized controlled trials and 2 quasi–randomized controlled trials, which were identified as meeting protocol-specified inclusion criteria, totaling 2079 patients (Tables 1 and 2).

Treatment Effectiveness

Chemotherapy combined with Chinese herbal medicine, compared with chemotherapy alone, significantly improved survival at 12 months (RR, 1.55; 95% CI, 1.39-1.72; $P < .000$; Figure 1), 24 months (RR, 2.15; 95% CI, 1.75-2.64; $P < .000$; Figure 2), and 36 months (RR, 2.76; 95% CI, 1.95-3.91; $P < .000$; Figure 3). Tumor response was also significantly improved (RR, 1.39; 95% CI, 1.24-1.56; $P < .000$; Figure 4). There were no reliable data indicating significant survival improvement at 6 months since there was significant between-study heterogeneity (Table 3; figure not shown).

We identified 2 studies that used the exact same herbal formula (Hua Chan Su) and conducted a separate meta-analysis.[16,17] The result also showed survival benefits of Hua Chan Su at 12 months (RR, 1.67; 95% CI, 1.38-2.02; $P < .000$; Table 3; figure not shown). It should be noted that Hua Chan Su contains bufotoxin, a digoxin-like substance that must be provided in carefully measured dosages to avoid cardiac glycoside toxicity.

A Chinese-English translation table is provided as an appendix, which identifies the original names of herbal formulas as identified in included studies and the names as translated into English.

Conclusions

Our meta-analysis data suggest promising evidence that Chinese herbal medicine in the treatment of HCC may have potential therapeutic value. Herbal medicine combined with chemotherapy for the treatment of HCC can improve survival at 12, 24, and 36 months when compared with chemotherapy alone. There is additional evidence that 6-month survival may also be improved; however, this finding is limited by the presence of between-study heterogeneity. Tumor response was also improved by the addition of Chinese herbal medicine to chemotherapy.

Table 1. Characteristics of Eligible Trials for This Meta-analysis

Study	No. Patients Enrolled		Mean Age (Median), y		Stage (Average size in cm^2)	Enrollment Interval, y	Jadad	Statistical Comparison	KPS		Comparison Treatment vs Control
	Treatment	Control	Treatment	Control					Treatment	Control	
Cao and Tang, 2003[20]	29	38	50.0	51.0	II, III	2000-2002	0	Yes			TAE-herbs vs TAE
Chen et al, 2001[21]	42	41	49.0	49.0	II, III	1998-2000	1	Yes			TAE-herbs vs TAE
Feng, 2002[22]	35	33	50.5	51.0	II, III	1997-2001	1	Yes	>60	>60	TACE-herbs vs TACE
Gao, 2004[23]	20	20	53.5	54.7	I, II	1998-2003	1	Yes	70	71	HACE-herbs vs HACE
Jia et al, 2003[24]	34	32			T3-4M0N0	2000-2002	1	Yes	>60	>60	TACE-herbs vs TACE
Li et al, 1998[25]	34	31			II, III	1993-?	3	Yes	60-90	60-90	HAI-herbs vs HAI
Li, 2001[26]	62	44	46.0	48.0	II, III	1997-2000	1	No			TACE/TAI-herbs vs TACE/TAI
Li and Li, 2001[27]	45	20	54.5	55.3	II, III	1994-?	1	Yes	≥40	≥40	IVC-herbs vs IVC
Liu and Zhu, 2002[28]	32	38	(47.0)	(48.0)			1	No			TACE-herbs vs TACE
Shao et al, 2001[29]	30	30	48.6	51.3	II, III	1996-1999	1	Yes			HACE-herbs vs HACE
Sun et al, 2002[16]	118	118	51.4	51.4		1994-2000	1	Yes			TACE-herbs vs TACE
Tian et al, 2001[30]	23	20	52.8	51.6	II, III	1998-?	1	Yes	60-80	60-80	HACE-herbs vs HACE
Wang, 1998[31]	36	36	48.3	46.5	I, II, III	1993-1996	1	Yes			HACE-herbs vs HACE
Wang et al, 2001[32]	63	44	48.0	49.0	III, IV	1997-?	0	Yes			TACE-herbs vs TACE
Wu et al, 2000[17]	36	44	52.4	50.5	II, III	1996-1997	1	Yes			TAE-herbs vs TAE
Wu, 1999[33]	13	12	55.0	56.0	II	1994-1998	1	Yes			TACE-herbs vs TACE
Wu et al, 2001[34]	25	25	53.1	49.3	I, II, III		1	Yes	≥60	≥60	TACE-herbs vs TACE
Wu et al, 2002[35]	30	30	51.5	52.3	II, III (56)	1998-2000	1	Yes	64.5	64.5	TAE-herbs vs TAE
Xie et al, 2004[36]	42	34	48.3	43.6	II, III	2000-?	1	Yes			IVC-herbs vs IVC
Yu, 2002[37]	29	31	(40.3)	(40.3)	II, III (56)	1999-?	1	No			TACE-herbs vs TACE
Zhang and Zhang, 1998[38]	30	28	60.0	61.0	III, IV		1	Yes			HAI-herbs vs HAI
Zhang et al, 1996[39]	30	27	51.0	49.0	I, II		1	No			TAI + TAE-herbs vs TAI + TAE
Zhang, 1998[40]	80	80	54.5	53.3	II, III		1	Yes	>60	>60	HAI-herbs vs HAI
Zhou et al, 2002[41]	26	20	50.0	49.5	II, III		1	No			TAE-herbs vs TAE
Zhou et al, 2002[42]	118	110	(48.0)	(47.5)	II, III	1990-1999	2	No			TACE-herbs vs TACE
Zhou et al, 1999[43]	15	16	57.7	57.7		1995-1997	1	No			IVC-herbs vs IVC

TACE/TAE = transcatheter arterial chemoembolization or transcatheter arterial embolization; TAI = transcatheter arterial infusion; HAI = hepatic arterial infusion; HACE = hepatic arterial chemoembolization; IVC = intravenous chemotherapy.

a. For specific definitions of the staging system used, see the respective reference(s).

Table 2. Chinese Herbal Medicines and Chemotherapy Drugs Used in Included Studies

Study	*Chemotherapy Drugs*	*TCM Formula*	*Ingredients*[a]
Cao and Tang, 2003[20]	Epi-ADM or THP-ADM, CBP, MMC, lipiodol	Ai Di Zhu She Ye	Panax ginseng, Astragalus membranaceus, Eleutherococcus senticosus, Mylabris cichorii
Chen et al, 2001[21]	ADM, DDP, 5-Fu, MMC, lipiodol, gelatin sponge	Pei Yuan Gu Ben Kang Ai Jiao Nang	Panax ginseng, Corydalis bulbosa, Curcuma phaeocaulis, Salvia miltiorrhiza, Momordica charantia, Euchresta japonica, Astragalus membranaceus, Ganoderma lucidum, Platycladus orientalis, Polyporus umbellatus, Houttuynia cordata, Poria cocos, Bupleurum chinense, Crataegus cuneata, Angelica polymorpha, Sargassum siliquastrum, Eleutherococcus senticosus, Scutellaria barbata, Hedyotis diffusa, Ziziphus spinosa, Rabdosia rubescens, Buthus martensii, Strychnos nux-vomica, Mylabris cichorii, Cremastra variabilis, Cervus elaphus
Feng, 2002[22]	CPT, DDP, 5-Fu, lipiodol	Xiao Yao San + Liu Jun Zi Tang/Yi Guan Jian/Ge Xia Zhu Yu Tang[b]	
Gao, 2004[23]	DDP, 5-Fu, MMC, lipiodol	Gan Ai Jian Ji	Astragalus membranaceus, Atractylodes macrocephala, Coix lacryma-jobi, Akebia trifoliata, Actinidia chinensis, Crataegus cuneata, Corydalis tuber, Bupleurum chinense, Curcuma aromatica, Artemisia scoparia
Jia et al, 2003[24]	ADM, DDP, MMC (or 5-Fu), lipiodol, gelatin sponge	Brucea javanica oil	Brucea javanica oil
Li et al, 1998[25]	ADM (or MMC), DDP (or CBP), 5-Fu	Gan Kang Chong Ji	Pseudostellaria heterophylla, Atractylodes macrocephala, Astragalus membranaceus, Angelica polymorpha, Panax notoginseng, Actinidia chinensis, Akebia trifoliata, Trionyx sinesis, Manis pentadactyla
Li, 2001[26]	THP-ADM, 5-Fu, MMC, lipiodol	Ge Xia Zhu Yu Tang/Xiao Yao San/Yin Chen Wu Ling San/Zi Shui Qing Gan Yin	Prunus persica, Paeonia suffruticosa, Cyperus rotundus, Carthamus tinctorius, Citrus aurantium, Salvia miltiorrhiza, Picrorhiza scrophulariifolia, Hedyotis diffusa, Bupleurum chinense, Melia toosendan, Paeonia lactiflora, Angelica polymorpha, Poria cocos, Atractylodes macrocephala, Astragalus membranaceus, Hedyotis diffusa, Scutellaria barbata, Artemisia scoparia, Rheum officinale, Gardenia jasminoides, Poria cocos, Alisma orientalis, Polyporus umbellatus, Atractylodes macrocephala, Phellodendron amurense, Hedyotis diffusa, Scutellaria barbata, Rehmannia glutinosa, Cornus officinalis, Dioscorea opposita, Poria cocos, Paeonia suffruticosa, Ligustrum lucidum, Eclipta prostrata, Hedyotis diffusa
Li and Li, 2001[27]	5-Fu, CF	Fu Zheng Yi Liu Tang	Astragalus membranaceus, Cinnamomum cassia, Polygonatum chinense, Rehmannia glutinosa, Pseudostellaria heterophylla, Atractylodes macrocephala, Coix lacryma-jobi, Angelica polymorpha, Paeonia lactiflora, Sparganium stoloniferum, Curcuma phaeocaulis, Hedyotis diffusa, Ligusticum chuanxiong, Salvia miltiorrhiza
Liu and Zhu, 2002[28]	ADM, DDP, 5-Fu, lipiodol	Yan Shu Zhu She Ye	Sophora flavescens, Euphorbia fischeriana, Angelica polymorpha, Smilax glabra
Shao et al, 2001[29]	ADM, DDP, 5-Fu, MMC, lipiodol or gelatin sponge	Gan Ai Yi Hao	Astragalus membranaceus, Codonopsis pilosula, Poria cocos, Ganoderma lucidum, Stephania tetrandra, Rehmannia glutinosa, Ligustrum lucidum, Eclipta prostrata, Salvia miltiorrhiza, Ligusticum chuanxiong, Buthus martensii, Curcuma phaeocaulis, Dioscorea opposita, Cremastra variabilis, Coix lacryma-jobi, Bupleurum chinense, Hedyotis diffusa, Scutellaria barbata, Paris polyphylla var. chinensis, Akebia quinata, Curcuma aromatica, Crataegus cuneata.
Sun et al, 2002[16]	Epi-ADM, CBP, MMC, lipiodol	Hua Chan Su	Bufotoxin
Tian et al, 2001[30]	DDP, 5-Fu, THP, lipiodol	Fu Zheng Jie Du Tang	Codonopsis pilosula, Astragalus membranaceus, Dioscorea opposita, Coix lacryma-jobi, Bupleurum chinense, Polygonum cuspidatum, Akebia trifoliata, Ligustrum lucidum, Eclipta prostrata
Wang, 1998[31]	ADM, CBP, MMC, iophendylate	Combination	Astragalus membranaceus, Poria cocos, Lycium barbarum, Ligustrum lucidum, Glycyrrhiza glabra var. glandulifera

(continued)

Table 2 (continued)

Study	*Chemotherapy Drugs*	*TCM Formula*	*Ingredients*[a]
Wang et al, 2001[32]	ADM, 5-Fu, MMC, lipiodol	Fu Zheng Hua Ji Jie Du Fang	Armeniaca mume, Crataegus cuneata, Panax ginseng, Atractylodes macrocephala, Trionyx sinesis, Sophora japonica, Poria cocos, Cornus officinalis, Coix lacryma-jobi, Scutellaria barbata, Cremastra variabilis, Smilax glabra
Wu et al, 2000[17]	DDP, 5-Fu, MMC, lipiodol, gelatin sponge	Hua Chan Su	Bufotoxin
Wu, 199933	CBP, 5-Fu, MMC	Yi Guan Jian Jia Wei	Adenophora verticillata, Codonopsis pilosula, Lycium barbarum, Melia toosendan, Angelica polymorpha, Ophiopogon japonicus, Rehmannia glutinosa, Hedyotis diffusa, Atractylodes macrocephala, Polyporus umbellatus, Solanum nigrum, Prunella vulgaris, Pinellia ternata, Cirsium spicatus, Ostrea cucullata, Salvia miltiorrhiza
Wu et al, 2001[34]	DDP, 5-Fu, MMC (or ADM), lipiodol, gelatin sponge	Ping Xiao Jiao Nang	Curcuma species, Agrimonia eupatoria, Citrus aurantium
Wu et al, 2002[35]	ADM (or CBP), 5-Fu, MMC, lipiodol, gelatin sponge	Hu Gan Ruan Jian Fang	Codonopsis pilosula, Astragalus membranaceus, Poria cocos, Hedyotis diffusa, Rabdosia serra, Atractylodes macrocephala, Curcuma aromatica, Bupleurum chinense, Trionyx sinesis, Alisma orientalis, Salvia miltiorrhiza, Scolopendra subspinipes
Xie et al, 2004[36]	ADM, 5-Fu, MMC	Ruan Gan Jian	Trionyx sinesis, Manis pentadactyla, Placenta hominis, Polygonatum chinense, Astragalus membranaceus, Sparganium stoloniferum, Curcuma phaeocaulis, Solanum nigrum, Paeonia lactiflora, Hedyotis diffusa, Paris polyphylla var. chinensis
Yu, 2002[37]	ADM, DDP, 5-Fu, lipiodol	Combination	Melia toosendan, Corydalis bulbosa, Saussurea lappa, Curcuma aromatica, Paris polyphylla var. chinensis, Curcuma phaeocaulis, Prunus persica, Carthamus tinctorius, Panax notoginseng, Ranunculus ternatus, Pinellia ternata, Bulbostemma paniculatum, Papaver somniferum, Artemisia scoparia, Rheum officinale, Lobelia radicans, Cynanchis paniculata, Panax quinquefolium, Ophiopogon japonicus, Schisandra chinensis, Poria cocos, Dioscorea opposita
Zhang and Zhang, 1998[38]	ADM + 5-Fu or DDP + MMC	Zi Ni Fu Gan Tang	Astragalus membranaceus, Polygonatum chinense, Codonopsis pilosula, Atractylodes macrocephala, Poria cocos, Ligustrum lucidum, Citrus reticulata, Ophiopogon japonicus, Cornus officinalis, Hedyotis diffusa, Glycyrrhiza glabra var. glandulifera
Zhang et al, 1996[39]	ADM, DDP, MMC	AC-III Zhu She Ye	Not specified
Zhang, 1998[40]	ADM, 5-Fu, MMC, lipiodol	Bu Gan Ruan Jian Tang	Manis pentadactyla, Asparagus species, Trionyx sinesis, Dendrobium monielforme, Ostrea cucullata, Agrimonia eupatoria, Codonopsis pilosula, Scutellaria barbata, Sargassum siliquastrum, Lagenaria siceraria var. microcarpa, Ganoderma lucidum, Buthus martensii, Panax notoginseng
Zhou et al, 2002[41]	ADM, 5-Fu, MMC, lipiodol, gelatin sponge	Ping Xiao Jiao Nang + Sophora japonica injection	Curcuma species, Agrimonia eupatoria, Citrus aurantium, Sophora japonica
Zhou et al, 2002[42]	ADM, DDP, 5-Fu, MMC, lipiodol (or gelatin sponge)	Liu Jun Zi Tang	Pseudostellaria heterophylla, Atractylodes macrocephala, Poria cocos, Glycyrrhiza glabra var. glandulifera, Pinellia ternata, Citrus reticulata, Astragalus membranaceus, Coix lacryma-jobi, Gallus gallus domesticus, Crataegus cuneata, Massa fermentata, Mantis pentadactyla, Trionyx sinesis
Zhou et al, 1999[43]	ADM, 5-Fu, MMC	Fu Zheng Xiao Liu He Ji	Panax ginseng, Astragalus membranaceus, Ligustrum lucidum, Xanthium sibiricum, Cremastra variabilis, Smilax glabra, Fritillaria thunbergii, Sophora japonica, Curcuma phaeocaulis, Manis pentadactyla, Hirudo nipponia, Scolopendra subspinipes

TCM = traditional Chinese medicine; ADM = Adriamycin; THP-ADM = pirarubicin hydrochloride; CBP = carboplatin; MMC = Mitomycin; 5-Fu = fluorouracil; DDP = cisplatin; CPT = Camptosar.
a. We use the term *Chinese herbal medicine* broadly to designate the traditional formulas or their modern revisions, as some of the products included in this review are animal in origin.
b. Because more than 30 individual herbs were combined in this study, we have noted here the names of the combination formulas in which they are found.

Table 3. Results

End Point	No. of Studies	No. of Patients	Relative Risk	95% Confidence Interval	Significance	Publication Bias	Heterogeneity
6-mo survival							
All studies combined	13	974	1.25	1.11, 1.40	$P < .000$[a]	$P < .000$	$P = .03$
12-mo survival							
All studies combined	17	1480	1.55	1.39, 1.72	$P < .000$[a]	$P = .03$	$P = .94$
Hua Chan Su	2	316	1.67	1.38, 2.02	$P < .000$[a]		$P = .90$
24-mo survival							
All studies combined	11	1082	2.15	1.75, 2.64	$P < .000$[a]	$P = .45$	$P = .77$
36-mo survival							
All studies combined	8	818	2.76	1.95, 3.91	$P < .000$[a]	$P = .94$	$P = .63$
Tumor response							
All studies combined	18	1369	1.39	1.24, 1.56	$P < .000$[a]	$P = .01$	$P = 1.00$

a. Significant treatment effect.

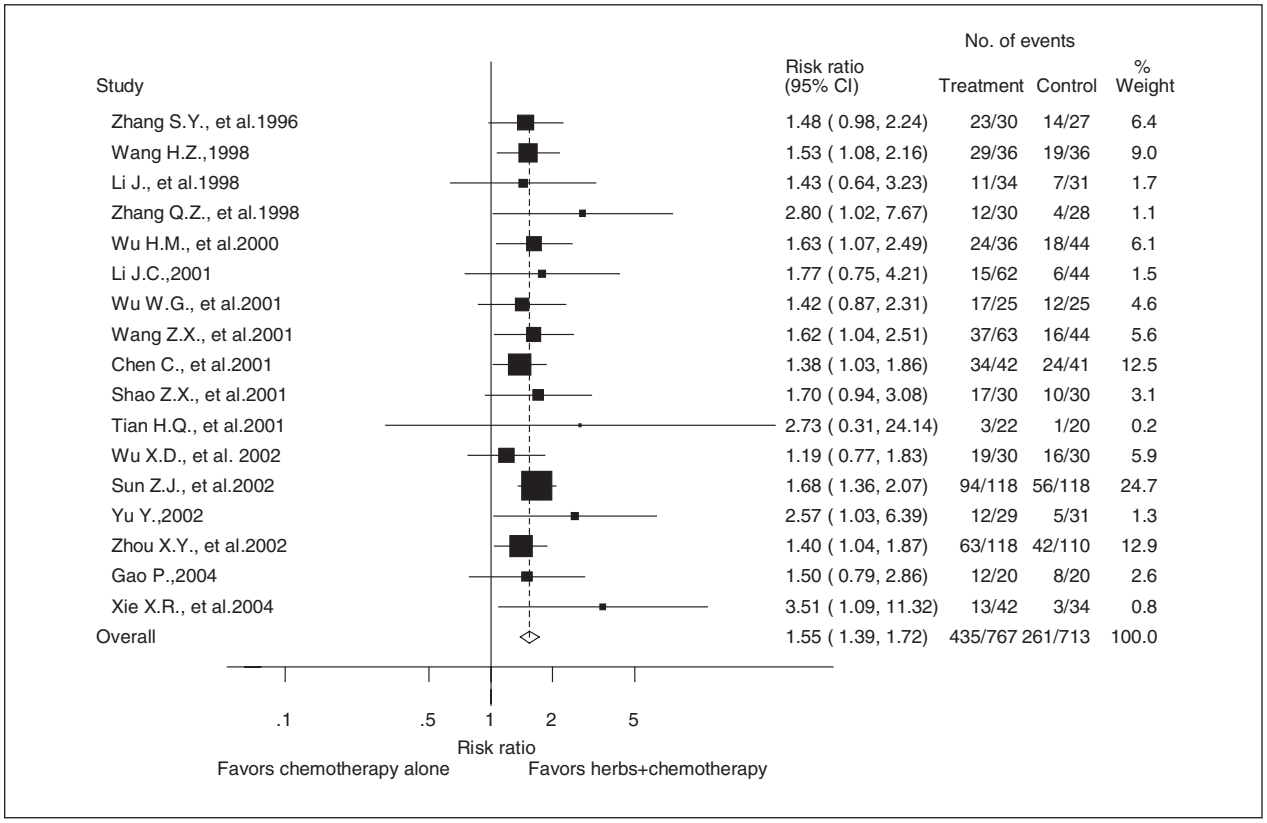

Figure 1 Twelve-month survival: herbs + chemotherapy versus chemotherapy alone.

In a separate meta-analysis of the only 2 studies using the exact same herbal medicine, Hua Chan Su, we found that 12-month survival was also increased.[16,17]

Limitations

Publication bias. We found evidence for publication bias in the data for meta-analysis of survival at 6 and 12 months for all herbal formulas combined. We also found evidence for publication bias in the data for meta-analysis of tumor response.

Research techniques used in Chinese studies. Because the studies we found were of generally poor quality, we are unable to make definite conclusions from our data. Published studies from China were found to be more highly condensed than typical articles published in the Western literature, with key details of study design omitted, especially details concerning blinding of subjects and clinicians. In addition, since most studies did not describe subject withdrawals or dropouts, it is not possible to adjust the analysis for censoring, and therefore pooled estimates of survival should be interpreted with caution. However, inadequate reporting

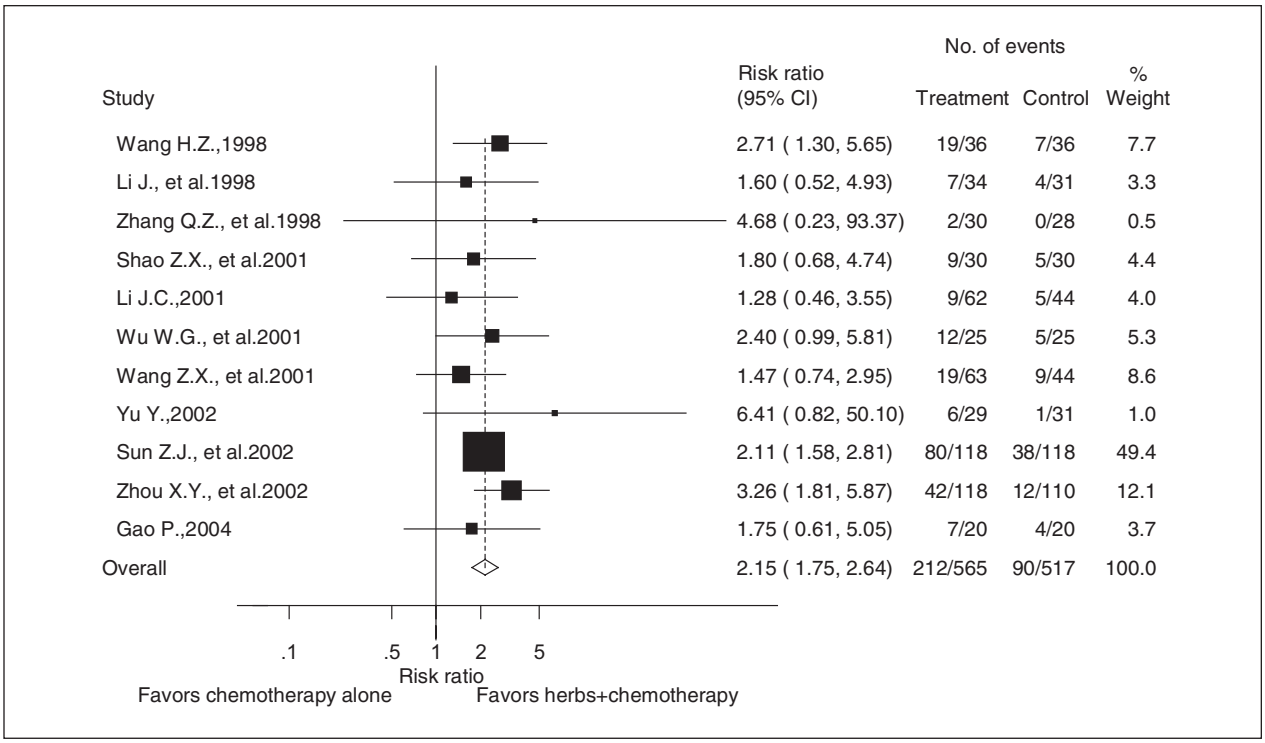

Figure 2 Twenty-four-month survival: herbs + chemotherapy versus chemotherapy alone.

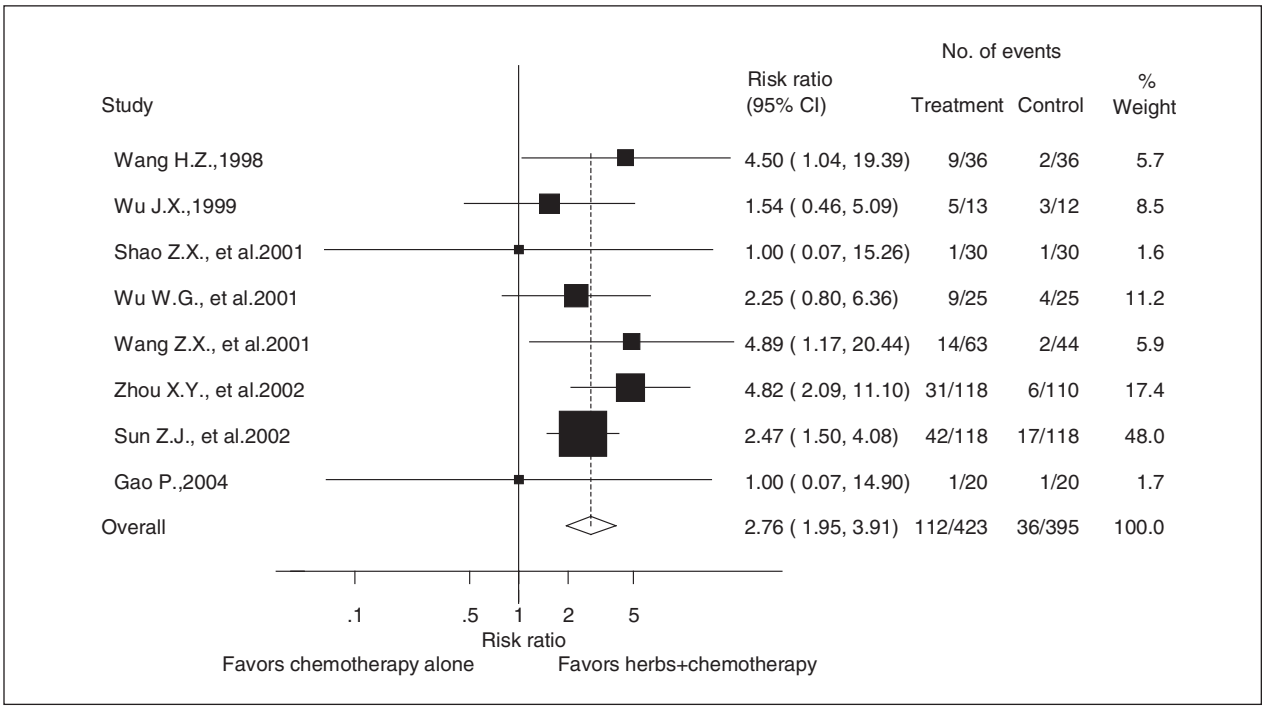

Figure 3 Thirty-six-month survival: herbs + chemotherapy versus chemotherapy alone.

of specific details of randomization is also found in many Western medical journals. In 2004, 8 years after publication of the CONSORT Statement (intended to improve the quality of reporting of results in randomized controlled trials), more than 40% of trials published in Western medical journals failed to use

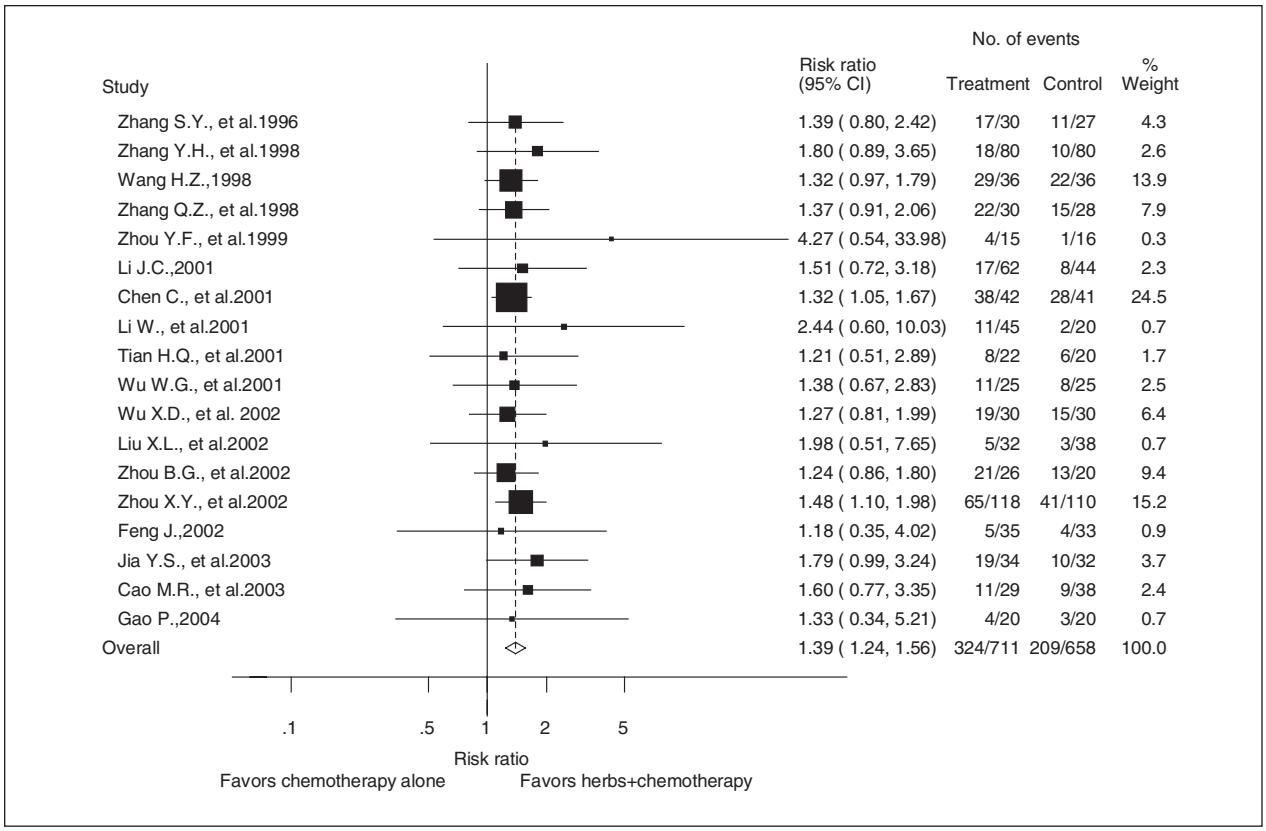

Figure 4 Tumor response: herbs + chemotherapy versus chemotherapy alone.

adequate randomization methods or failed to report the method for concealment of allocation.[18] In 1994, this figure was as high as 70% to 80%.[19]

An additional comment on the issue of blinding in these studies is warranted. Most of the studies (20 of 26) assessed in this meta-analysis provided the treatment group with orally administered Chinese herbal medicine combined with intravenous chemotherapy and the control group only intravenous chemotherapy. Therefore, blinding of subjects and clinicians was not possible. In such a study design setting, blinding could be achieved only if the treatment and control groups received both oral and intravenous trial medications (ie, the treatment group was given true orally administered herbal medicine and intravenous chemotherapy and the control group was given placebo orally administered herbal medicine and intravenous chemotherapy).

In future trials, we propose that Chinese investigators employ relatively simple measures such as random number–generating software for use in randomization and placebo trial drugs for use in comparing different therapies or in evaluating new and emerging extracted active components of Chinese herbal medicines. More thorough reporting of patients' characteristics and accounting for patient withdrawals and dropouts would also be helpful.

Standardized herbal formulas. Since there is no standard Chinese formula for the treatment of HCC, it is hard to identify the active components in the treatments. Further investigation is needed on effects of Chinese herbal medicine on HCC, on the identity of active components of Chinese herbal medicine, and on the therapeutic mechanisms underlying possible survival benefits of combining Chinese herbal medicine with chemotherapy for HCC.

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APPENDIX
English-Chinese Table of Herbal Formula Names

English	Chinese
AC-III Zhu She Ye	AC-III注射液
Ai Di Zhu She Ye	艾迪注射液
Brucea javanica oil	鸦胆子油乳
Bu Gan Ruan Jian Tang	补肝软坚汤
Combination	中医辨证治疗
Fu Zheng Hua Ji Jie Du Fang	扶正化积解毒方
Fu Zheng Jie Du Tang	扶正解毒汤
Fu Zheng Xiao Liu He Ji	扶正小瘤合剂
Fu Zheng Yi Liu Tang	扶正抑瘤汤
Gan Ai Jian Ji	肝癌煎剂
Gan Ai Yi Hao	肝癌一号
Gan Kang Chong Ji	肝康冲剂
Ge Xia Zhu Yu Tang	膈下逐瘀汤
Hu Gan Ruan Jian Fang	护肝软坚方
Hua Chan Su	华蟾素
Liu Jun Zi Tang	刘君子汤
Pei Yuan Gu Ben Kang Ai Jiao Nang	培元固本抗癌胶囊
Ping Xiao Jiao Nang	平消胶囊
Ruan Gan Jian	软肝煎
Sophora japonica injection	苦参素
Xiao Yao San	逍遥散
Yan Shu Zhu She Ye	岩舒注射液
Yi Guan Jian	一贯煎
Yi Guan Jian Jia Wei	一贯煎加味
Yin Chen Wu Ling San	茵陈五苓散
Zi Ni Fu Gan Tang	自拟复肝汤
Zi Shui Qing Gan Yin	滋水清肝饮

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