World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i13.3843

World J Gastroenterol 2015 April 7; 21(13): 3843-3849
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma

Myeong Jun Song

Myeong Jun Song, Division of Hepatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Daejeon 301-723, South Korea
Author contributions: Song MJ solely contributed to this paper.
Conflict-of-interest: There is no conflict of interest.

Correspondence to: Myeong Jun Song, MD, PhD, Division of Hepatology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Daeheung-ro 64, Jung-gu, Daejeon 301-723, South Korea. mjsong95@gmail.com
Telephone: +82-42-2209291
Received: November 24, 2014
Peer-review started: November 25, 2014
First decision: December 26, 2014
Revised: January 2, 2015
Accepted: February 5, 2015
Article in press: February 5, 2015
Published online: April 7, 2015

Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Surgery, percutaneous ablation and liver transplantation are the only curative treatment modalities for HCC. However, the majority of patients have unresectable disease at diagnosis. Therefore, effective treatment options for patients with advanced HCC are required. In advanced HCC, according to current international guidelines, sorafenib, a molecular targeted agent, is the standard treatment. However, alternative treatment modalities are required because of the low response rates and unsuitability of molecular agents in real practice. In various treatment modalities, mostly in Asia, hepatic arterial infusion chemotherapy (HAIC) has been applied to advanced HCC with a view to increasing the therapeutic efficacy. HAIC provides direct drug delivery into the tumor feeding vessels and also minimizes systemic toxicities through a greater first-pass effect in the liver. However, the sample sizes of studies on HAIC have been small and large randomized trials are still lacking. In this article, we describe the treatment efficacy of HAIC for advanced stage HCC and discuss future therapeutic possibilities.

Key words: Hepatocellular carcinoma; Advanced stage hepatocellular carcinoma; Sorafenib; Hepatic arterial infusion chemotherapy; Treatment efficacy

Core tip: Sorafenib is the standard of treatment for advanced hepatocellular carcinoma (HCC). However, the suitability of sorafenib is limited by its low response rates, and unsuitability for patients with poor liver function. Therefore, other treatment modalities are required. Hepatic arterial infusion chemotherapy (HAIC) has the advantages of delivering high levels of chemotherapeutic drugs directly into tumor-associated hepatic arterial branches and repeat injections are relatively simple to carry out. Thus the local therapeutic level is increased and systemic adverse effects are decreased. In the future, HAIC may be a promising treatment strategy for the management of advanced HCC.

Song MJ. Hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma. *World J Gastroenterol* 2015; 21(13): 3843-3849 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i13/3843.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i13.3843

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and shows high cancer-related mortality worldwide[1]. The incidence of HCC is increasing with the prevalence of major risk factors such as hepatitis B, hepatitis C, alcohol and nonalcoholic steatohepatitis. Despite surveillance programs in high-risk patients, most patients with HCC are diagnosed at an advanced stage. In limited patients (fewer than 30%), curative treatments, including resection, liver transplantation, or radiofrequency ablation, can be applied[2]. The prognosis of patients with HCC is still poor, and life expectancy is difficult to predict[3]. Furthermore, advanced HCC patients may show heterogeneous clinical features, from single nodules associated with limited portal vein thrombosis, to multiple intrahepatic metastasis associated with extrahepatic spread[4,5].

Sorafenib, the multi-tyrosine kinase inhibitor, was reported to show survival benefits and is the current standard treatment in advanced HCC[6,7]. Sorafenib treatment has shifted the treatment strategy towards molecular targeted therapies for advanced HCC[8]. However, other alternative treatment modalities are required because of low response rates[9] and the unsuitability of molecular agents in real clinical practice.

In other alternative therapies, hepatic arterial infusion chemotherapy (HAIC) has been applied to advanced stage HCC with a view to increasing the therapeutic efficacy in Japan and Korea. HAIC provides direct delivery of chemotherapeutic agents into tumor feeding vessels and also minimizes systemic toxicities through a greater first-pass effect in the liver[10,11]. Therefore, the purpose of this article was to describe the treatment efficacy of HAIC for advanced stage HCC and discuss future therapeutic possibilities.

HEPATIC ARTERY INFUSION CHEMOTHERAPY

HAIC has been applied to treat advanced HCC patients with tumors that are unresectable, refractory to TACE in single or multiple tumors, the infiltrative type or those with portal vein thrombosis. Theoretically, HAIC shows better efficacy than systemic chemotherapy in advanced HCC because the infusion of the chemotherapeutic agents through the hepatic artery provides direct delivery of high concentrations of drugs to the feeding arteries of HCC. In addition, HAIC also minimizes systemic toxicities through a greater first-pass effect in the liver, reflecting the lower the systemic levels of the drugs compared to systemic infusion. HAIC has been applied in advanced stage HCC with a view to improving the therapeutic indexes in Asia, especially Japan and Korea. However, there is no evidence for a survival benefit of HAIC compared with sorafenib.

Various chemotherapeutic agents based on 5-fluorouracil (5-FU) and cisplatin are commonly used and have been investigated for HAIC[12,13]. The mechanisms of the 5-FU are the disruption of RNA synthesis and inhibition of the nucleotide synthetic enzyme thymidylate synthase by active metabolites of 5-FU, including fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate and fluorouridine triphospate[14]. Cisplatin also shows cytotoxic effects and reinforces the effect of 5-FU[8,15]. The mechanism of cisplatin is the direct inhibition of DNA replication and interruption of methionine transport in cancer cells. Furthermore, cisplatin increases levels of intracellular folic acid, which is important for binding of FdUMP, an active metabolite of 5-FU to thymidylate synthetase[16,17]. Therefore, the synergistic effect of cisplatin and 5-FU is the basis of HAIC. While various treatment regimens based on 5-FU and cisplatin have been tried in HAIC[18,19] , few comparative trials for these regimens have been evaluated in advanced HCC patients.

TECHNICAL ASPECT

To evaluate hepatic artery vascularization and patency of portal vein, angiography of the celiac trunk and superior mesenteric artery were performed through access to the femoral artery. Any reflux of anti-cancer drugs into the gastrointestinal tract, and out of the liver, is a contraindication for HAIC. If necessary, embolization of non-tumor feeding vessels is performed to prevent the reflux of cytotoxic drugs into both uninvolved liver parenchyma and extrahepatic organs, such as the stomach and duodenum. After selection of the tumor feeding artery, the catheter was inserted at the proper hepatic or common hepatic artery and connected to the port system. The port device in a subcutaneous pocket was implanted in the right or left iliac fossa. An infusion pump is necessary to prevent the reflux of chemotherapeutic agents because of implantation of the infusion port in the hepatic artery (Figure 1).

TREATMENT OUTCOME

In 1995, Toyoda *et al*[20] reported the treatment outcome of HAIC in HCC patients with portal vein thrombosis as first. Transarterial chemoembolization (TACE) has long been used as a palliative therapy for unresectable HCC in real clinical practice. However, HAIC has shown favorable outcomes in patients with intractable, advanced HCC compared with TACE (Figures 2 and 3).

Sumie *et al*[21] reported a comparative study between TACE and HAIC in advanced HCC. The tumor response rates (objective response) of HAIC and TACE groups were 56.3% and 23.8%, respectively. In advanced HCC (TNM stage Ⅳ or the tumor maximal diameter > 5 cm), patients tended to show better

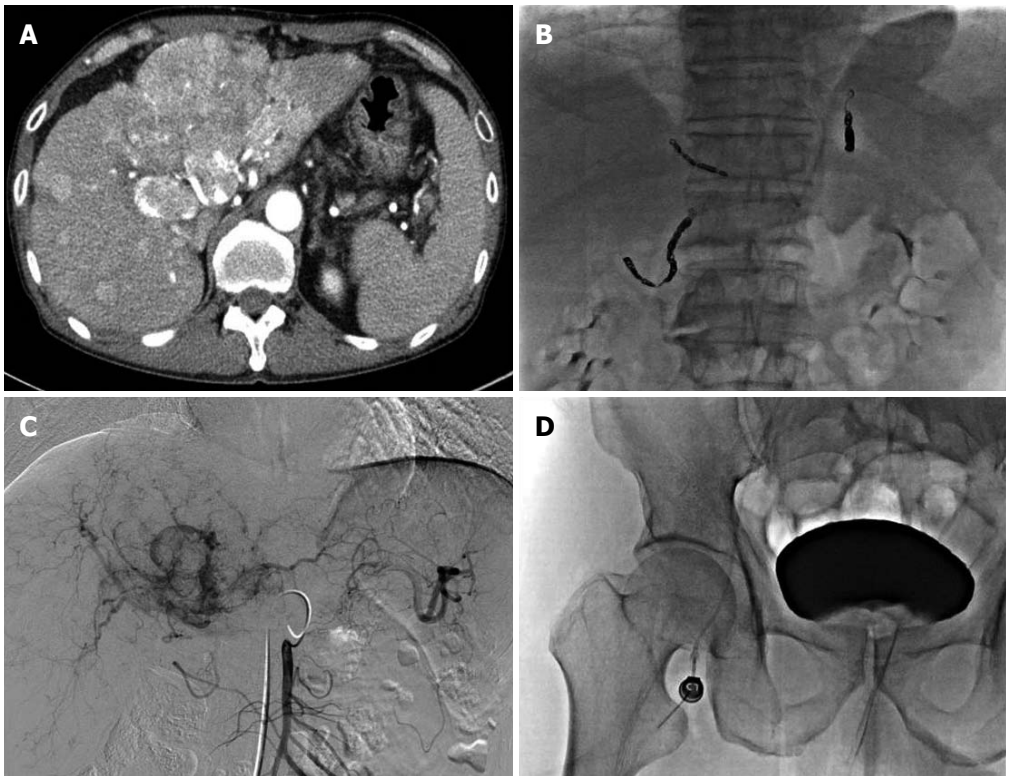

Figure 1 Technical aspects of hepatic artery infusion chemotherapy. A: Liver dynamic computed tomography showing multinodular hepatocellular carcinoma (HCC) with portal vein thrombosis; B: The embolization of non-target vessels to minimize the flow of chemotherapeutic agents into both uninvolved liver parenchyma and extrahepatic tissues; C: After finding HCC in the feeding artery, the tip of the catheter was located at the proper hepatic or common hepatic artery, chemotherapeutic agents were infused through a pump; D: The proximal end of the catheter was connected to the injection port, which was implanted in a subcutaneous pocket in the right iliac fossa.

survival benefits in the HAIC group than in the TACE group, although the overall survival rates between the two groups showed no significant difference. Kim *et al*[22] also reported that the objective response rate and overall survival in HAIC showed better than TACE group (16.7% *vs* 0%, $P = 0.030$, median survival; 193 *vs* 119 d, $P = 0.026$, respectively). In terms of adverse events, there were no significant differences between the HAIC and TACE group.

The reported overall response rate was 15%-56% (Table 1). Various combination regimens based on 5-FU and cisplatin have been investigated for HAIC. Hamada *et al*[23] reported treatment response and survival in HAIC using cisplatin (10 mg) and 5-FU (250 mg). The objective response rate was 17% (CR 1%, PR 16%). The median survival time was 19.5 mo. Lin *et al*[24] prospectively evaluated the effect of HAIC of the combination of cisplatin, mitomycin C, 5-FU and leucovorin. The treatment regimen consisted of cisplatin (10 mg/m^2), mitomycin C (2 mg/m^2), leucovorin (15 mg/m^2) and 5-FU (100 mg/m^2) for 5 consecutive days. The objective response was 28.3% (CR 9.4%, PR 18.9%). The patients with treatment response showed longer survival benefits than the patients without treatment response (24.6 *vs* 8.7 mo, $P < 0.001$). Hwang *et al*[25] evaluated the efficacy of HAIC using the FEM (5-FU, epirubicin, mitomycin C) regimen for advanced HCC. The regimen consisted of 5-FU (330 mg/m^2, every week), epirubicin (30 mg/m^2, every 4 wk) and mitomycin-C (2.7 mg/m^2, every 2 wk). The objective response was 38.9% and the median survival was 8 mo.

While various treatment regimens based on 5-FU and cisplatin have been tried in HAIC, few comparative trials for these regimens have been evaluated in advanced HCC patients. Recently, in a prospective study in Korea, Woo *et al*[26] reported a comparative study between high dose HAIC (5-FU, 500 mg/m^2 for 3 consecutive days and cisplatin, 60 mg/m^2 on day 2) and low dose HAIC (5-FU, 170 mg/m^2 and cisplatin, 7 mg/m^2 on days for 5 consecutive days). The objective response rate in the high-dose HAIC showed significantly better efficacy than the low-dose HAIC (16.7% *vs* 0%, $P = 0.024$). The median time to progression and overall survival showed more favorable trends in the high-dose HAIC group than in the low-dose HAIC group (145 *vs* 90 d, $P = 0.095$, 193 *vs* 153 d, $P = 0.108$, respectively). Furthermore, Kim *et al*[17] showed a better long-term outcome of high dose HAIC. During the follow-up period, overall survival and time to progression were 9.5 and 6.0 mo, respectively. These results seem comparable to the reported outcome of sorafenib.

A randomized phase Ⅱ trial by Yamashita *et al*[27] compared the response rates to treatment with interferon combined with HAIC using 5-FU and

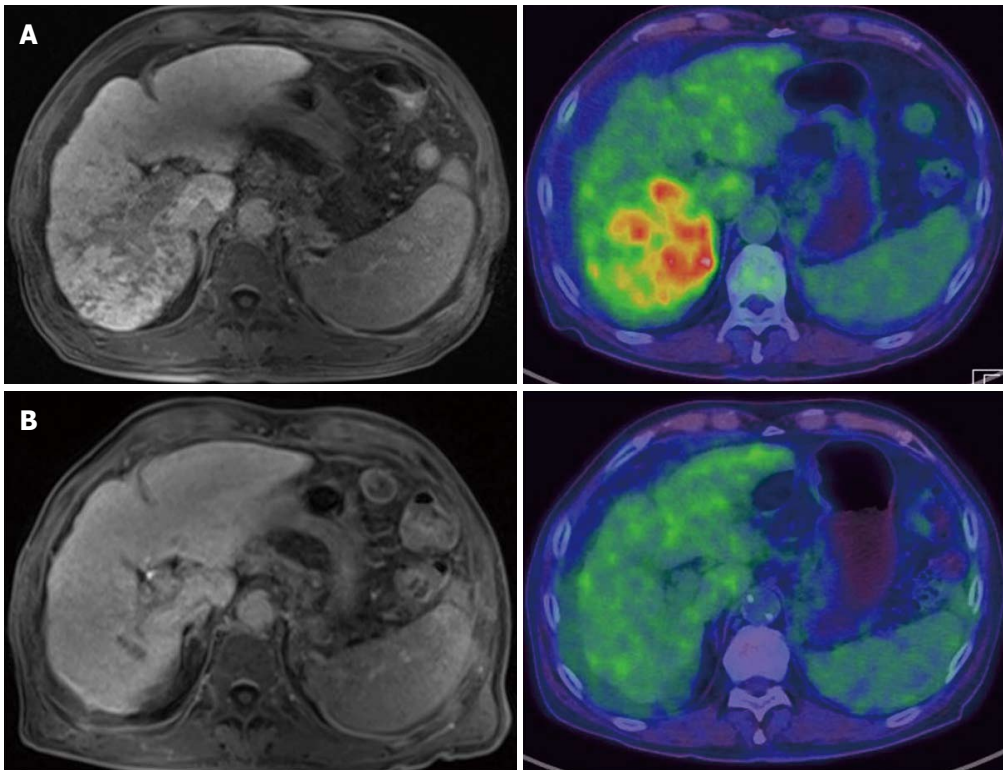

Figure 2 Favorable outcome of patient with infiltrative hepatocellular carcinoma treated by hepatic artery infusion chemotherapy. A: Patient with infiltrative type hepatocellular carcinoma (HCC) with portal vein thrombosis in liver dynamic magnetic resonance imaging (MRI) showed high FDG uptake; B: After hepatic artery infusion chemotherapy, this patient showed no viable HCC except focal portal vein thrombosis in a follow-up liver MRI and positron emission tomography/computed tomography.

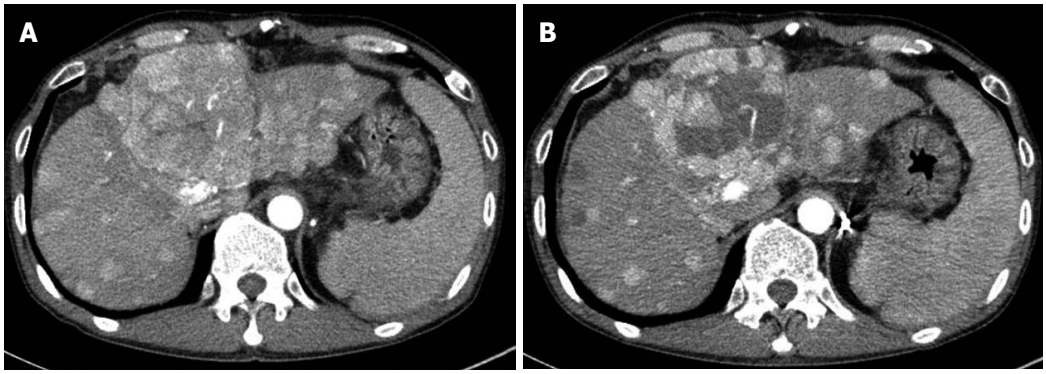

Figure 3 Favorable response of patient with multinodular hepatocellular carcinoma treated by hepatic artery infusion chemotherapy. A: Patient with multinodular type hepatocellular carcinoma (HCC) with portal vein thrombosis in baseline liver dynamic computed tomography (CT); B: After hepatic artery infusion chemotherapy, this patient showed partial necrosis of HCC in a follow-up liver dynamic CT.

cisplatin (IFN/FU + CDDP) or 5-FU (IFN/FU) alone. The response rates were 45.6% for the IFN/FU + CDDP group and 24.6% for the IFN/FU group (P = 0.030). Although there was no significant difference in overall survival, the progression free survival showed a better outcome in the IFN/FU+CDDP compared with the IFN/FU group (6.5 mo *vs* 3.3 mo, respectively, P = 0.0048).

Recently, Nouso *et al*[28] evaluated the efficacy of HAIC of 5-FU and cisplatin for advanced HCC in a nationwide survey in Japan. The outcome of 476 patients with HCC who underwent HAIC was compared with 1466 patients who did not receive active therapy. In propensity score-matched analysis, median survival in patients with HAIC was longer than that in patients with supportive care (14.0 *vs* 5.2 mo, respectively, P < 0.0001). Song *et al*[29] reported a comparative study between sorafenib and HAIC. The median overall survival in the HAIC treatment group was better than that in the sorafenib group (7.1 *vs* 5.5 mo, P = 0.011). Therefore, HAIC might show a survival benefit as well as reducing the tumor burden. However, most previous reports were retrospective designs. The small sample size and disparity in the treatment response of each institution are limitations.

Table 1 Treatment response and survival rate of hepatic arterial infusion chemotherapy

Group	No.	Treatment regimen	Response rate (CR + PR)	Median survival
Toyoda *et al*[20]	21	Cisplatin: 5-10 mg 5-FU: 500 mg	14.3%	36-549 d
Sumie *et al*[21]	16	Group 1: Cisplatin 10 mg + 5-FU : 250 mg (5 d)	56.3%	2.7 yr
	21	Group 2: TACE with epirubicin	23.8%	1.7 yr
Kim *et al*[22]	36	Group 1: 5-FU 500 mg/m^2 on D 1-3 + Cisplatin 60 mg/m^2 on D2	16.7% (PR16.7%)	193 d
	31	Group 2: TACE with doxorubicin (10-60 mg)	0%	119 d
Hamada *et al*[23]	88	Cisplatin: 10 mg 5-FU: 1000 mg	17% (CR1%/PR16%)	19.5 mo
Lin *et al*[24]	53	Cisplatin: 10 mg, 5-FU 100 mg, Mitomycin 2 mg Leucovorin 15 mg	28.3%	NA
Hwang *et al*[25]	18	5-FU 330 mg/m^2 every week Epirubicin 30 mg/m^2 Mitomycin-C 2.7 mg/m^2 every 2 wk	38.9% (PR 38.9%)	8 mo
Sim *et al*[30]	67	Group 1: Cisplatin: 80 mg/m^2 (1 d)	20% (CR2.5%/PR17.5%)	5 mo
	36	Group 2: Cisplatin: 60 mg/m^2 (1 d) + 5-FU 500 mg/m^2 (3 d)	19.2% (CR 3.8%/PR15.4%)	8.5 mo
Lim *et al*[31]	40	Group 1: Cisplatin 10 mg + 5-FU 250 mg (5 d)	3.8%(PR 3.8%)	5 mo
	39	Group 2: Conservative care	0%	3 mo
Woo *et al*[26]	36	Group 1 (High dose): 5-FU 500 mg/m^2 on D 1-3 + Cisplatin 60 mg/m^2 on D2	16.7% (PR 16.7%)	193 d
	32	Group 2 (Low dose): 5-FU 170 mg/m^2 on D 1-5 + Cisplatin 7 mg/m^2 on D 1-5	0%	153 d
Yamashita *et al*[27]	57	Group 1 (IFN/FU): 5-FU 300 mg/m^2 per day for 5 d for 1st 2 wk + IFNα-2b 3M U IM 3 times/wk for 4 wk	45.6% (CR 1.7%/PR 43.9%)	10.5 mo
	57	Group 2 (IFN/FU + Cisplatin): IFN/FU + Cisplatin 20 mg/m^2 on day 1, 8	24.6% (CR 5.3%/PR 19.3%)	17.6 mo
Nouso *et al*[28]	476	Group 1: Cisplatin + 5-FU	40.5% (CR 4.0%/PR 36.5%)	14.0 mo
	1466	Group 2: No therapy		5.2 mo
Song *et al*[29]	50	Group 1: Cisplatin + 5-FU ± epirubicin	24.0%	7.1 mo
	60	Group 2: Sorafenib	13.3%	5.5 mo

NA: Not available; 5-FU: 5-fluorouracil.

SAFETY AND COMPLICATION

The complications of using HAIC were reported as fever, jaundice, GI complication (nausea, vomiting or abdominal pain) and complication of port insertion site (infection and thrombosis). The rates of these post embolization complications in HAIC are lower than TACE. In particular, TACE may induce the following adverse effects: hepatic artery injury (stenosis or obstruction) or the development of collaterals, such as periportal or inferior phrenic artery. HAIC could be precluded by these complications. In some cases, hepatic or renal failure was reported. These cases may have been caused by underlying liver disease or disease progression rather than toxicity of HAIC.

CONCLUSION

Molecular targeting agents, including sorafenib, have been used and investigated clinically to treat advanced HCC. Although sorafenib treatment has shifted to the treatment strategy of molecular targeted therapies for advanced HCC, other alternative therapies are required because of the low response rates and unsuitability for patients with poor liver function. These studies may suggest the possibility of HAIC as an alternative therapy for advanced HCC. In particular, the indications for HAIC were unresectable, refractory to TACE in single or multiple tumors, infiltrative type or tumor with portal vein thrombosis. The advantages of HAIC are the delivery high doses of chemotherapeutic drugs directly into the hepatic arterial branches relating with the tumors and the ability to repeat the injection relatively simply, consequently increasing the local therapeutic level and decreasing systemic adverse effects. Therefore, HAIC may be a promising treatment strategy for the management of advanced HCC.

However, the limitations of this study on HAIC are that the sample size was small and that large randomized trials are still lacking. Further study to determination of appropriate treatment regimen in HAIC is important. As sorafenib is the standard treatment for advanced HCC, a comparative study between sorafenib and HAIC is needed. Currently, randomized controlled trials between HAIC and sorafenib in advanced HCC are ongoing to validate the overall clinical benefits of HAIC.

REFERENCES

1 **El-Serag HB**, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999; **340**: 745-750

[PMID: 10072408]
2 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430 [PMID: 11592607]
3 **Tandon P**, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. *Liver Int* 2009; **29**: 502-510 [PMID: 19141028]
4 **Mazzaferro V**, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013; **57**: 1826-1837 [PMID: 22911442 DOI: 10.1002/hep.26014]
5 **Song MJ**, Bae SH. Newer treatments for advanced hepatocellular carcinoma. *Korean J Intern Med* 2014; **29**: 149-155 [PMID: 24648795 DOI: 10.3904/kjim.2014.29.2.149]
6 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]
7 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/s1470-2045(08)70285-7]
8 **Yamasaki T**, Sakaida I. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma and future treatments for the poor responders. *Hepatol Res* 2012; **42**: 340-348 [PMID: 22151009 DOI: 10.1111/j.1872-034X.2011.00938.x]
9 **Shen YC**, Hsu C, Cheng AL. Molecular targeted therapy for advanced hepatocellular carcinoma: current status and future perspectives. *J Gastroenterol* 2010; **45**: 794-807 [PMID: 20567987 DOI: 10.1007/s00535-010-0270-0]
10 **Ganeshan A**, Upponi S, Hon LQ, Warakaulle D, Uberoi R. Hepatic arterial infusion of chemotherapy: the role of diagnostic and interventional radiology. *Ann Oncol* 2008; **19**: 847-851 [PMID: 18029972 DOI: 10.1093/annonc/mdm528]
11 **Park JY**, Ahn SH, Yoon YJ, Kim JK, Lee HW, Lee do Y, Chon CY, Moon YM, Han KH. Repetitive short-course hepatic arterial infusion chemotherapy with high-dose 5-fluorouracil and cisplatin in patients with advanced hepatocellular carcinoma. *Cancer* 2007; **110**: 129-137 [PMID: 17508408 DOI: 10.1002/cncr.22759]
12 **Ishikawa T**, Imai M, Kamimura H, Tsuchiya A, Togashi T, Watanabe K, Seki K, Ohta H, Yoshida T, Kamimura T. Improved survival for hepatocellular carcinoma with portal vein tumor thrombosis treated by intra-arterial chemotherapy combining etoposide, carboplatin, epirubicin and pharmacokinetic modulating chemotherapy by 5-FU and enteric-coated tegafur/uracil: a pilot study. *World J Gastroenterol* 2007; **13**: 5465-5470 [PMID: 17907289]
13 **Yoshikawa M**, Ono N, Yodono H, Ichida T, Nakamura H. Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. *Hepatol Res* 2008; **38**: 474-483 [PMID: 18430093 DOI: 10.1111/j.1872-034X.2008.00338.x]
14 **Longley DB**, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. *Nat Rev Cancer* 2003; **3**: 330-338 [PMID: 12724731 DOI: 10.1038/nrc1074]
15 **Nagano H**. Treatment of advanced hepatocellular carcinoma: intraarterial infusion chemotherapy combined with interferon. *Oncology* 2010; **78** Suppl 1: 142-147 [PMID: 20616597 DOI: 10.1159/000315243]
16 **Nishiyama M**, Yamamoto W, Park JS, Okamoto R, Hanaoka H, Takano H, Saito N, Matsukawa M, Shirasaka T, Kurihara M. Low-dose cisplatin and 5-fluorouracil in combination can repress increased gene expression of cellular resistance determinants to themselves. *Clin Cancer Res* 1999; **5**: 2620-2628 [PMID: 10499641]
17 **Kim BK**, Park JY, Choi HJ, Kim do Y, Ahn SH, Kim JK, Lee do Y, Lee KH, Han KH. Long-term clinical outcomes of hepatic arterial infusion chemotherapy with cisplatin with or without 5-fluorouracil in locally advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2011; **137**: 659-667 [PMID: 20552225 DOI: 10.1007/s00432-010-0917-5]
18 **Itamoto T**, Nakahara H, Tashiro H, Haruta N, Asahara T, Naito A, Ito K. Hepatic arterial infusion of 5-fluorouracil and cisplatin for unresectable or recurrent hepatocellular carcinoma with tumor thrombus of the portal vein. *J Surg Oncol* 2002; **80**: 143-148 [PMID: 12115797 DOI: 10.1002/jso.10116]
19 **Murata K**, Shiraki K, Kawakita T, Yamamoto N, Okano H, Nakamura M, Sakai T, Deguchi M, Ohmori S, Nakano T. Low-dose chemotherapy of cisplatin and 5-fluorouracil or doxorubicin via implanted fusion port for unresectable hepatocellular carcinoma. *Anticancer Res* 2003; **23**: 1719-1722 [PMID: 12820447]
20 **Toyoda H**, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T, Kiriyama S, Suga T, Takahashi M. The efficacy of continuous local arterial infusion of 5-fluorouracil and cisplatin through an implanted reservoir for severe advanced hepatocellular carcinoma. *Oncology* 1995; **52**: 295-299 [PMID: 7777243]
21 **Sumie S**, Yamashita F, Ando E, Tanaka M, Yano Y, Fukumori K, Sata M. Interventional radiology for advanced hepatocellular carcinoma: comparison of hepatic artery infusion chemotherapy and transcatheter arterial lipiodol chemoembolization. *AJR Am J Roentgenol* 2003; **181**: 1327-1334 [PMID: 14573429 DOI: 10.2214/ajr.181.5.1811327]
22 **Kim HY**, Kim JD, Bae SH, Park JY, Han KH, Woo HY, Choi JY, Yoon SK, Jang BK, Hwang JS, Kim SG, Kim YS, Seo YS, Yim HJ, Um SH. A comparative study of high-dose hepatic arterial infusion chemotherapy and transarterial chemoembolization using doxorubicin for intractable, advanced hepatocellular carcinoma. *Korean J Hepatol* 2010; **16**: 355-361 [PMID: 21415578 DOI: 10.3350/kjhep.2010.16.4.355]
23 **Hamada A**, Yamakado K, Nakatsuka A, Takaki H, Akeboshi M, Takeda K. Hepatic arterial infusion chemotherapy with use of an implanted port system in patients with advanced hepatocellular carcinoma: prognostic factors. *J Vasc Interv Radiol* 2004; **15**: 835-841 [PMID: 15297587 DOI: 10.1097/01.RVI.0000128815.35555.0E]
24 **Lin CP**, Yu HC, Cheng JS, Lai KH, Lo GH, Hsu PI, Lin CK, Chen HH, Lo CC, Liang HL, Tseng HH. Clinical effects of intra-arterial infusion chemotherapy with cisplatin, mitomycin C, leucovorin and 5-flourouracil for unresectable advanced hepatocellular carcinoma. *J Chin Med Assoc* 2004; **67**: 602-610 [PMID: 15779483]
25 **Hwang JY**, Jang BK, Kwon KM, Chung WJ, Park KS, Cho KB, Hwang JS, Ahn SH, Kim GC, Kim YH, Choi JS, Kwon JH. [Efficacy of hepatic arterial infusion therapy for advanced hepatocellular carcinoma using 5-fluorouracil, epirubicin and mitomycin-C]. *Korean J Gastroenterol* 2005; **45**: 118-124 [PMID: 15725716]
26 **Woo HY**, Bae SH, Park JY, Han KH, Chun HJ, Choi BG, Im HU, Choi JY, Yoon SK, Cheong JY, Cho SW, Jang BK, Hwang JS, Kim SG, Kim YS, Seo YS, Yim HJ, Um SH. A randomized comparative study of high-dose and low-dose hepatic arterial infusion chemotherapy for intractable, advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2010; **65**: 373-382 [PMID: 19763572 DOI: 10.1007/s00280-009-1126-2]
27 **Yamashita T**, Arai K, Sunagozaka H, Ueda T, Terashima T, Yamashita T, Mizukoshi E, Sakai A, Nakamoto Y, Honda M, Kaneko S. Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma. *Oncology* 2011; **81**: 281-290 [PMID: 22133996]
28 **Nouso K**, Miyahara K, Uchida D, Kuwaki K, Izumi N, Omata M, Ichida T, Kudo M, Ku Y, Kokudo N, Sakamoto M, Nakashima O, Takayama T, Matsui O, Matsuyama Y, Yamamoto K. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer* 2013; **109**: 1904-1907

[PMID: 24008659 DOI: 10.1038/bjc.2013.542]
29 **Song DS**, Song MJ, Bae SH, Chung WJ, Jang JY, Kim YS, Lee SH, Park JY, Yim HJ, Cho SB, Park SY, Yang JM. A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *J Gastroenterol* 2014; Epub ahead of print [PMID: 25027973 DOI: 10.1007/s00535-014-0978-3]
30 **Sim MK**, Kim DY, Park JY, Kim JK, Kim SA, Ahn SH, Chon CY, Moon YM, Won JY, Lee DY, Han KH. [Efficacy of repeated hepatic arterial infusion chemotherapy in advanced hepatocellular carcinoma with portal vein tumor thrombosis]. *Korean J Hepatol* 2005; **11**: 268-274 [PMID: 16177553]
31 **Lim TY**, Cheong JY, Cho SW, Sim SJ, Kim JS, Choi SJ, Choi JW, Kwon HC, Lee KM, Kim JK, Won JH, Yoo BM, Lee KJ, Hahm KB, Kim JH. [Effect of low dose 5-fluorouracil and cisplatin intra-arterial infusion chemotherapy in advanced hepatocellular carcinoma with decompensated cirrhosis]. *Korean J Hepatol* 2006; **12**: 65-73 [PMID: 16565607]

P- Reviewer: Celikbilek M, Morales-Gonzalez JA **S- Editor**: Qi Y
L- Editor: Stewart G **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327