European Review for Medical and Pharmacological Sciences 2016; 20: 2872-2877

Transarterial chemoembolization with degradable starch microspheres (DSM-TACE): an alternative option for advanced HCC patients? Preliminary results

R. IEZZI[1], M. POMPILI[2], M. NESTOLA[1], M. SICILIANO[2], E. ANNICCHIARICO[2], M.A. ZOCCO[2], E. RINNINELLA[2], A. POSA[1], G.E.M. ANTONUCCIO[1], A. GASBARRINI[2], L. BONOMO[1]; AND HEPATOCATT STUDY GROUP

[1]Department of Radiological Sciences, Institute of Radiology, "A. Gemelli" Hospital, Catholic University of the Sacred Heart, School of Medicine, Rome, Italy

[2]Department of Internal Medicine, "A. Gemelli" Hospital, Catholic University, Rome, Italy

Abstract. – OBJECTIVE: To assess safety, feasibility and effectiveness of transarterial chemoembolization with degradable-starch-microspheres (DSM-TACE) in the treatment of patients with advanced hepatocellular carcinoma (HCC) dismissing or ineligible for multikinase-inhibitor chemotherapy administration (Sorafenib) due to unbearable side effects or clinical contraindications.

PATIENTS AND METHODS: Six consecutive advanced HCC patients dismissing Sorafenib because of unbearable side effects or worsened clinical conditions were enrolled in our prospective single-center pilot study. DSM-TACE was performed via a lobar approach, based on extent and distribution of the disease (1 treatment session for every lobe involved, with a 2-week interval in case of bilobar disease). Tumor response based on mRECIST criteria was evaluated on MD-CT performed at 1 month after "complete treatment" and every 3 months thereafter.

RESULTS: Eleven treatments were performed, and technical success was achieved in all patients. No intra/peri-procedural death/major complications occurred. No signs of liver failure or systemic toxicity were detected. At one month follow-up, 5 partial responses (83.3%) and 1 progression disease (16.6%) with an overall disease control (ODC) of 83.3% were observed. In two patients with ODC and residual viable tumor higher than 50%, a repeated DSM-TACE treatment was performed. During the mean follow-up of 11 months (range: 4-14 months), an ODC of 66.6% was obtained. Progression-free survival was 5.5 months with a cumulative 6-month and 1-year overall survival rates of 83.3% and 66.6%, respectively.

CONCLUSIONS: DSM-TACE seems to be a promising option for advanced HCC patients ineligible for Sorafenib administration or dismissing it due to progressive disease or unbearable side effects.

Key Words
HCC, Chemoembolization, TACE, Advanced, Degradable microspheres, DSM-TACE

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths in the world[1-3]. Child-Pugh A-B cirrhotic patients with HCC are classified as stage C according to the Barcelona Clinic Liver Cancer (BCLC) staging system if they show cancer related symptoms according to the Eastern Cooperative Oncology Group (ECOG), macrovascular invasion or extrahepatic spread (lymph node involvement or metastases)[4,5]. These patients bear a dismal prognosis, with expected median survival times of 6 months, or an overall survival of 25% at 1-year and the only therapy showing a significant survival benefit is represented by Sorafenib, a Raf-, vascular endothelial growth factor (VEGF) receptor-, platelet-derived growth factor (PDGF) receptor-blocking multikinase tyrosine inhibitor[6]. Indeed, the SHARP Investigators Study Group, and thereafter the Asia Pacific trial, demonstrated that Sorafenib significantly prolongs time to progression without significant differences concering median time to symptomatic progression [7,8]. Moreover, the SHARP Investigators Study Group reported an overall occurrence of treatment-related adverse events as high as 80% in the Sorafenib group (predominantly gastrointestinal, constitutional, or dermatologic and grading 1 or 2 in severity but leading to permanent treatment discontinuation in 11% of cases)[7]. However, to date, there is no

Corresponding Author: Roberto Iezzi, MD; e-mail: roberto.iezzi@rm.unicatt.it

approved treatment in BCLC C patients dismissing or ineligible for Sorafenib treatment; based on this background, it would be useful to find an effective alternative treatment option[9].

This aim could be achieved through the clinical development of transarterial chemoembolization with degradable starch microspheres (DSM-TACE) (EmboCept®S 50 μm microspheres, 450 mg/7.5 ml Pharmacept). In detail, Embocept consists of a suspension of starch microspheres loaded or unloaded with doxorubicin that are rapidly and completely degradable by liver α-amylase within 25-40 minutes from the arterial infusion, allowing a temporary occlusion of the arterial microcirculation at the tumor level[10-12].

The aim of this pilot study was to evaluate the safety, feasibility, and effectiveness of DSM-TACE in patients with advanced HCC, ineligible for Sorafenib administration due to clinical contraindication or dismissing it for unbearable side effects or progressive disease.

Patients and Methods

Study design/Study population

This is a prospective single-center phase II pilot study to test the safety, feasibility, and efficacy of DSM-TACE. The study was conducted according to the protocol and the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice and was approved by our local Ethics Committee. Informed consent was obtained from all subjects prior to any treatment.

All patients were evaluated by a multidisciplinary tumor board composed by all medical specialists involved in HCC patients' management (hepatologist, oncologist, hepatic and transplant surgeon, nuclear physician, radiotherapist, radiologist and interventional radiologist).

Requirements for inclusion were: (a) advanced BCLC-C HCC in patients dismissing or ineligible to Sorafenib administration, (b) liver cirrhosis classified as Child-Pugh score A or B. The exclusion criteria were: (a) Child-Pugh score C, (b) performance status (ECOG) > 2, (c) platelet count < 40,000/μL and/or international normalized ratio >1.5, (d) severe renal impairment or serum creatinine levels ≥ 2 mg/dl, (e) doxorubicin administration contraindications. Vascular invasion, as well as non-neoplastic portal vein thrombosis, were not considered exclusion criteria.

Treatment

DSM-TACE was always performed in an angiography suite with monitoring of vital signs and anesthesia care, by an interventional radiologist with more than 10 years of experience in interventional procedures at the beginning of the study. The treatment was performed under local anesthesia through a femoral approach, with a Seldinger needle, by using a 5Fr 12-cm arterial introducer sheath (Terumo, Tokyo, Japan). The selective celiac trunk catheterization and the cannulation of common hepatic artery were performed with a 5Fr diagnostic catheter (Cobra, Simmons; Terumo, Tokyo, Japan). A hepatic angiography was then obtained to identify the appropriate anatomy of the hepatic artery and any possible branches related to non-target structures, and exclude any arteriovenous fistulae. After diagnostic angiography, a selective lobar catheterization was performed with a coaxial technique, placing a 2.7Fr microcatheter (Progreat; Terumo, Tokyo, Japan) in the right or left hepatic artery that was feeding the involved lobe. A selective lobar angiography was then performed to confirm the correct position of microcatheter, to identify/protect non-hepatic arteries and limit any possible extrahepatic diffusion of the treatment. In particular, identification of cystic artery was recommended to ensure that the catheter tip would bypass this anatomical point.

Under fluoroscopic guidance, a solution of 7.5 ml of Embocept loaded with 50 mg of Epirubicin (Farmorubicin® 50 mg Powder), followed by 2.5 ml of unloaded Embocept was slowly and continuously infused until a "stop flow" was observed.

All the patients received antibiotics to prevent infections the day before and after treatment, for a total of seven days. According to the extent and distribution of disease, a single or a double treatment was planned. In particular, patients with monolobar disease underwent a single treatment session whereas patients with bilobar disease underwent two treatment sessions with a 2-week interval between sessions[13].

End-points and post treatment follow up studies

The objective of the study was to test the safety, feasibility, and effectiveness of DSM-TACE in cirrhotic patients with advanced HCC. A technical success was defined as the ability to deliver the full 7.5 mL planned dose (i.e., 50 mg of Epirubicin-loaded microspheres) and to obtain a stop flow. Primary endpoints were the assessment

of safety, evaluated as the occurrence of major/minor complications, and overall disease control (ODC), calculated as the sum of objective responses and stable diseases. Secondary endpoints were progression-free survival (PFS) and overall survival (OS).

Perioperative morbidity and mortality, included major/minor complications and death occurring within 7 days from treatment, were registered. Major complication was defined as an event that engenders substantial morbidity and disability, an increased level of care, or substantially lengthens hospital stay. All other complications were considered minor[14].

Treatment efficacy based on α-fetoprotein dosage and mRECIST criteria, in terms of complete response (CR), partial response (PR), stable disease (SD) and local tumor progression (TP), was evaluated on Multiphasic CT exam performed 4 ± 1 weeks after complete treatment and every 3 months thereafter[13,14].

Results

Patients characteristics

Between December 2013 and March 2014, 6 consecutive BCLC C patients, with advanced HCC dismissing or ineligible for Sorafenib administration, were enrolled. The main features of patients and tumors are reported in Table I. All patients had advanced multifocal HCC and were classified as BCLC C due to macrovascular invasion (2 patients) or ECOG status 1 (4 patients). Four patients dismissed Sorafenib administration due to side effects (2 patients: gastrointestinal symptoms - grade 2 diarrhea) or progressive disease (2 patients) during Sorafenib administration. The last two patients were considered ineligible for Sorafenib administration because of deteriorated liver function (total bilirubin higher than 2 mg/dl).

Treatment Feasibility and Tolerance

A total of 11 treatments in 6 patients were performed. Technical success was achieved in all patients; in particular, in all treatments, it was possible to deliver the full 7.5 mL planned dose and to obtain a stop flow.

No major complications were registered. Minor complications were detected in 2 patients (33.3%) and were represented by increased serum level of transaminases and transient cholecystitis completely recovered without any therapy.

Table I. Demographic and clinical characteristics of study population.

Male	6	100%
Female	0	0%
Age (ys)	168.5 ± 10.4	
Cirrhosis etiology		
Hepatitis B	0	0%
Hepatitis C	4	66.6%
Alcohol-related	1	16.6%
Cryptogenetic	1	16.6%
Extension disease		
Unilobar	1	20%
Bilobar	5	80%
Previous surgery		
No	5	90%
Yes (right hepatectomy)	1	10%
Vascular invasion		
Yes	2	40%
No	4	60%
Mild ascites		
Yes	3	50%
No	3	50%
Child-Pugh class		
A	3	50%
B7	1	16.6%
B8-9	2	33.3%
Total bilirubin (mg/dL): ≤1.0		
≤2.0	4	66,6%
>2	2	33.3%
Albumin (g/dL)		
>3.5	3	50%
<3.5	3	50%
Alanine aminotransferase (IU/L)		
≥40	5	83.4%
≤40	1	16.6%

Tumor Response

On 1-month CT, five partial responses (PR 83.3%, 5/6) and 1 progression disease (PD 16.6%, 1/6) with an overall disease control of 83.3% were observed. According to these results, a repeated DSM-TACE schedule treatment was performed in 2 patients with residual viable tumor volume higher than 50%. During the mean follow-up period of 11 months (range: 5-14 months), an overall disease control was detected in 4/6 patients (2PR and 2SD, 66.6%) while the 2 remaining patients showed PD (Figure 1).

PFS and Overall Survival rate

PFS, calculated using the Kaplan-Meier method, was 5.5 months. The cumulative 6-month and 1-year OS were 83.3% and 66.6%, respectively (Figure 2).

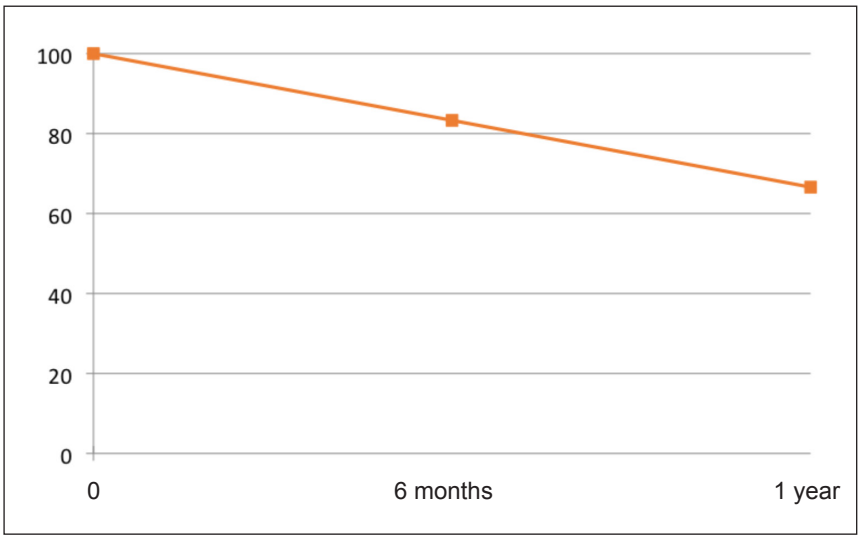

Figure 1. Overall survival rate.

Discussion

Sorafenib administration is considered the only treatment option available for well-moderately compensated cirrhotic patients with advanced HCC – staged as BCLC stage C – or with tumor progressing after loco-regional therapies. However, Sorafenib has no effects on the symptomatic time to progression, and several patients experience treatment-related adverse events leading to permanent treatment discontinuation in about 11% of cases[7,8,15-21]. Furthermore, some patients can not be referred to this therapy because of severe comorbidities. There is no approved alternative for these patients who can only be addressed to the best supportive care and bear a dismal prognosis with a cumulative 1-year survival of 25%[6].

Based on this background, we conducted a single-center pilot study using DSM-TACE in BCLC C HCC patients ineligible to or dismissing Sorafenib. TACE with Degradable Starch Microspheres (Embocept) allows the temporary occlusion of the smaller arterial vessels, improving the therapeutic effect (by reducing the immediate wash-out of the cytostatic agent), and decreasing the risk of systemic toxicity and post-embolic syndrome. This treatment was safe and effective in this setting of patients, achieving an ODC of 66.6%, a PFS of 5.5 months and a 1-year OS rate of 66.66% (Table II). No major complications were experienced even if the study group was a high-risk population for standard TACE; in particular, 2 patients had portal vein thrombosis, 3 were Child-Pugh B class (1 B7, 2 B8-9), and 2 of them had a total bilirubin level higher than 2 mg/dl. Furthermore, the transitory vascular occlusion generated by DSM allowed to repeat treatment in more than 30% of patients, reducing the risk of liver toxicity that may occur when repeating conventional TACE [10-12,15]. Finally, DSM-TACE was not offset by any important side effects or worsening of liver function; in detail, no patient experienced an increased Child-Pugh score 1 month after treatment.

When dealing with other potential treatment options in these setting of patients, Yttrium-90 transarterial radioembolization (TARE) should have to be considered. However, its role in patients with advanced HCC is currently still under investigation and to the best of our knowledge there are no published data on its use in BCLC C patients excluded from Sorafenib therapy due to side effects or serum bilirubin level > 2 mg/dL suggesting impending liver function failure. Both DSM-TACE and TARE may be used in HCC patients with macroscopic vascular invasion and act by selectively delivering high-dose anticancer treatments directly to the tumor, with a limited embolic effect, so improving the toxicity profiles and decreasing the risk of treatment-related worsening of liver function.

Future randomized prospective comparative studies performed on larger population are needed to define adequate patient selection criteria and long-term results of these therapeutic techniques. An interesting point favouring DSM-TACE could be its lower cost when compared to TARE.

The main limitation of our pilot study is the small number of patients enrolled. However, this paper is a technical note, mainly aimed at defining the feasibility and safety of DSM-TACE in BCLC C HCC patients.

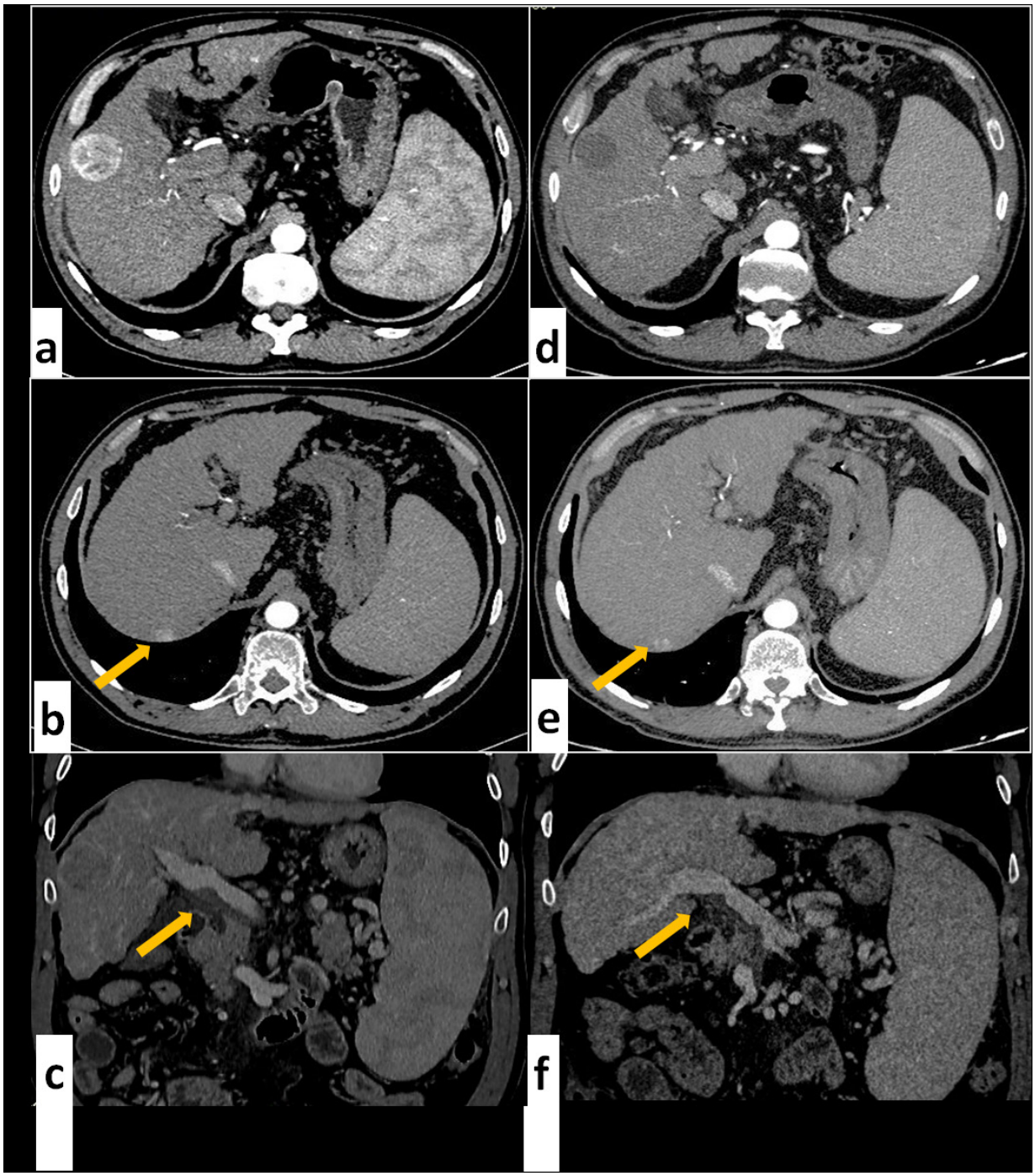

Figure 2. C.G.G, ♂, 52yo. Patient with advanced multinodular HCC: main lesion of 3.7 cm in sV (a) and 1 cm in sVII (*arrow in b*) with concomitant neoplastic portal vein thrombosis (c). Two right lobar DSM-TACE were performed with a 4-weeks interval. 6-months CT control (d-f) demonstrated complete necrosis of the main nodule in sV and of the multiple nodules in the right lobe and stability of the lesion in the sVII segment (e) and of the portal vein thrombosis (f). We obtained a substantial downstaging of disease and the patient underwent liver transplant.

Conclusions

DSM-TACE seems to be a safe, technically feasible and well-tolerated effective treatment option for advanced HCC patients ineligible for Sorafenib administration or dismissing it due to unbearable side effects. Further investigations with larger patient populations and longer follow-up are warranted.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

References

1) Rinninella E, Zocco MA, De Gaetano A, Iezzi R, Campanale M, Cesario V, Barbaro F, Ponziani FR, Caracciolo G, Triarico S, Tortora A, Ianiro G, Gasbarrini A. From small nodule t o overt HCC: a multistep process of carcinogenesis as seen during surveillance. Eur Rev Med Pharmacol Sci 2012; 16: 1292-1294.
2) Murata S, Mine T, Sugihara F, Yasui D, Yamaguchi H, Ueda T, Onozawa S, Kumita S. Interventional treatment for unresectable hepatocellular carcinoma. World J Gastroenterol 2014; 20: 13453-13465.
3) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer stat. CA Cancer J Clin 2011; 61: 69-90.
4) Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-338.
5) Falkson G, MacIntyre JM, Moertel CG, Johnson LA, Scherman RC. Primary liver cancer. An Eastern Cooperative Oncology Group Trial. Cancer 1984; 54: 970-977.
6) Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology 2010; 51: 1274-1283.
7) 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; SHARP Investigators study group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.
8) 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.
9) Biolato M, Marrone G, Racco S, Di Stasi C, Miele L, Gasbarrini G, Landolfi R, Grieco A. Transarterial chemoembolization (TACE) for unresectable HCC: a new life begins? Eur Rev Med Pharmacol Sci 2010; 14: 356-362.
10) Wiggermann P, Wohlgemuth WA, Heibl M, Vasilj A, Loss M, Schreyer AG, Stroszczynski C, Jung EM. Dynamic evaluation and quantification of microvascularization during degradable starch microspheres transarterial Chemoembolization (DSM-TACE) of HCC lesions using contrast enhanced ultrasound (CEUS): a feasibility study. Clin Hemorheol Microcirc 2013; 53: 337-348.
11) Niessen C, Unterpaintner E, Goessmann H, Schlitt HJ, Mueller-Schilling M, Wohlgemuth WA, Stroszczynski C, Wiggermann P. Degradable starch microspheres versus ethidol and doxorubicin in transarterial chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2014; 25: 240-247.
12) Yamasaki T, Hamabe S, Saeki I, Harima Y, Yamaguchi Y, Uchida K, Terai S, Sakaida I. A novel transcatheter arterial infusion chemotherapy using iodized oil and degradable starch microspheres for hepatocellular carcinoma: a prospective randomized trial. J Gastroenterol 2011; 46: 359-366.
13) Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30: 52-60.
14) Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236.
15) European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943.
16) Cabrera R, Nelson DR. Review article: the management of hepatocellular carcinoma. Aliment Pharmacol Ther 2010; 31: 461-476.
17) Llovet JM, Bruix J. Molecular targeted therapies in hepatocellular carcinoma. Hepatology 2008; 48: 1312-1327.
18) Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.
19) Chan SL, Mok T, Ma BB. Management of hepatocellular carcinoma: beyond sorafenib. Curr Oncol Rep 2012; 14: 257-266.
20) Wong R, Frenette C. Updates in the management of hepatocellular carcinoma. Gastroenterol Hepatol 2011; 7: 16-24.
21) Peck-Radosavljevic M. Drug therapy for advanced-stage liver cancer. Liver Cancer 2014; 3: 125-131.