Epirubicin is more effective than miriplatin in balloon-occluded transcatheter arterial chemoembolization for hepatocellular carcinoma

Tomotake Shirono[a] Hideki Iwamoto[a, b] Takashi Niizeki[a] Shigeo Shimose[a] Masahito Nakano[a] Manabu Satani[a] Naoki Kamachi[a] Ryoko Kuromatsu[a] Toru Kuwano[a] Masatoshi Tanaka[c] Syuusuke Okamura[a] Yu Noda[a] Miwa Sakai[a] Mika Nomiyama[a] Hironori Koga[a] Takuji Torimura[a]

a Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; b Iwamoto Medical Clinic, Kitakyusyu, Japan; c Yokokura Hospital, Omuta, Japan

Running title: Comparison of Epirubicin and Miriplatin in therapeutic effects of B-TACE

Keywords: balloon-transcatheter arterial chemoembolization, epirubicin, miriplatin, hepatocellular carcinoma

Correspondence and Reprint requests to Hideki Iwamoto MD, PhD

67 Asahi-machi, Kurume City, Fukuoka 830-0011, Japan.

e-mail: iwamoto_hideki@med.kurume-u.ac.jp

Abstract

Background

Transcatheter arterial chemoembolization (TACE) is a standard therapy for intermediate hepatocellular carcinoma (HCC). Recently, balloon-occluded TACE (B-TACE) has been developed.

Purpose

The aim of this study was to clarify the effects of B-TACE for HCC patients. Especially, we focused on the optimal anticancer drug which should be used in B-TACE.

Methods

We retrospectively analyzed 35 patients with HCC who received B-TACE and evaluated effects of B-TACE. And factors which associated with enhanced TTP in B-TACE were evaluated by univariate and multivariate analysis.

Results

Total 35 HCC patients/ 40 nodules were treated with B-TACE between June 2013 and August 2016. 25 nodules were treated by epirubicin and the rest 15 was miriplatin. Overall survival of the patients treated with B-TACE was 26.4 months and time to progression of the treated lesions was 8.1 months. Overall TE4 rate, i.e.

100% necrosis rate, of B-TACE was 52.5%. Achievement of TE4 and TACE naïve case were independent significant factors which associated with better TTP of B-TACE. To achieve TE4 by B-TACE, epirubicin and TACE naïve case were significant factors. TE4 rate of each regimen, i.e. epirubicin and miriplatin, was 64% and 33%.

Conclusion

Epirubicin was more effective than miriplatin as the anticancer drug used in B-TACE.

Introduction

Transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) was firstly reported in 1970's by Yamada et al[1] and has become a standard therapy for intermediate HCC [2-4]. Anticancer drugs suspended with lipiodol, oil-based radio-opaque contrast agent, are injected through tumor feeding artery, following by gelatin sponge particles are to embolize in conventional TACE (c-TACE) [5-7]. Epirubicin, doxorubicin, cisplatin or miriplatin are often used as representative chemotherapeutic agents in c-TACE[8].

In some cases, c-TACE cannot be effectively demonstrated its performance. For example, hypovascular tumor is one of them. The injected drugs on c-TACE cannot distribute into tumor because of weak blood flow into tumor or narrow tumor feeding artery. To solve the problem, microballoon-catheter was developed[9]. TACE using microballoon catheter, which is called balloon-occluded TACE (B-TACE), is attracting attention as a new procedure in TACE. Several reports show that B-TACE is able to increase accumulation of lipiodol emulsion within tumor than c-TACE, which contributes to improvement of local control for treated HCC[10-12].

Miriplatin hydrate (Dainippon Sumitomo Pharma Co. Osaka, Japan),

which has the same structure as oxaliplatin, is a lipophilic derivative that can be well suspended in lipiodol[13, 14]. Miriplatin has high sustained-release performance, which could contribute to maintenance of high drug concentration within tumor, theoretically. Miriplatin is often used on B-TACE according to the previous reports[9, 15, 16]. However, Miyayama et al. has reported that miriplatin showed higher local recurrence rate on c-TACE, compared with epirubicin[17] and other report also showed that the effect of miriplatin is inferior to that of the other drug in c-TACE[17, 18]. Therefore, there is still room for further discussion for which anticancer drugs should be used on B-TACE procedures.

This study is a retrospective singlecenter study which evaluated the therapeutic effects and safety of B-TACE. Especially, we have analyzed which anticancer drugs should be selected on B-TACE for treatment of HCC.

Material and Methods

Study design and patients

This is a retrospective study for the patients with HCC who received B-TACE at singlemedical center from June 2013 to September 2014. The study was approved by the ethical committee of Kurume University School of Medicine. The

data regarding with B-TACE were collected from three independent medical centers, Kurume University School of Medicine, Chikugo City Hospital and Yokokura Hospital. During this period, 774 angiography regarding with treatment of HCC have been performed. 339 cases of them are TACE and B-TACE are performed for 35 cases of them. We have excluded the nodules less than 10 mm for evaluation. Therefore, 40 nodules were assessed as the nodules treated with B-TACE, which is expressed as the targeted lesions.

B-TACE procedures

Under local anesthesia, 4 French (Fr) sheath was inserted into common femoral artery. Celiac artery and common hepatic artery were catheterized with 4 Fr catheter and disital subtraction angiography (DSA) was performed with non-iodine contrast agent. After evaluation of tumor location, 2.8 Fr microballoon-catheter (Logos, Piolax Inc, Kanagawa, Japan or ATTENDANT, Terumo, Tokyo, Japan) was inserted into the target artery which perfused into tumor locating sub- or sub-sub- hepatic segment. After insertion into the target artery, we have performed DSA to evaluate tumor location, tumor hemodynamics without and with balloon-filtration due to 0.2 ml mixture of the contrast medium

and the heparin-added physiological saline.

We have selected the anticancer drug for suspending with lipiodol on demand. When we selected epirubicin (Nippon kayaku, Tokyo, Japan), 30 mg of epirubicin was dissolved in 2 ml saline and suspended with adapted amount of lipiodol. When we selected miriplatin (Dainippon Sumitomo Pharma Co. Ltd, Osaka, Japan), 60 mg of miriplatin was suspended with adapted amount of lipiodol. Maximum amount of lipiodol was 10 ml for suspension. All drug preparation have been performed according to the manufacturers' recommended protocol. After balloon-infiltration, each lipiodol suspended drug was slowly injected until placed catheter pushed back because of its increased pressure. After injection of lipiodol, one millimeter of gelatin sponge agent (Gelpart, Nippon Kayaku, Tokyo, Japan) was injected to embolize the targeted artery.

Follow-up process and assessment of response

As the first follow-up, enhanced CT was performed 1 month after the initial treatment. Imaging examination for each patient was performed according to the same protocol. For CT examination, three contrast phases were performed after pre-contrast scans. All CT scans were taken by more than 64 raw systems. After the

first follow-up, regular imaging follow-up was performed every two to three month. Scanned images were read and diagnosed by two radiologists and one hepatologist. Local radiological response of the targeted lesions was assessed according to the Response Evaluation Criteria in Cancer of the Liver (RECICL) criteria[19, 20]. TE4 means tumor necrosis of 100% or 100% reduction in tumor size. TE3 is tumor necrosis 50-100% or 50-100% reduction in tumor size. TE1 is tumor enlargement of more than 25%. TE2 is between TE3 and TE1. And objective response rate (RR) was defined as TE4 plus TE3, while disease control rate (DCR) was defined as RR plus TE2. RR and DCR on the maximal effects were assessed. Time to progression (TTP) of the targeted lesions was defined as the period from the date of B-TACE to the date which showed TE1 in regular radiological examination after B-TACE.

Safety and complications evaluation

Adverse events (AEs) were monitored and recorded. AEs were assessed during treatment and follow-up period. AEs were assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical Analysis

All statistical analyses were carried out by JMP statistical analysis software (JMP pro version 11, Tokyo, Japan). Overall survival (OS) and TTP was calculated by Kaplan-Meier method and analyzed by log-rank test. The factors associated with better TTP or achievement of TE4 were evaluated univariate and multivariate analysis by peason's chi-square test and Cox proportional hazards model. Variables associated ($p<0.10$) with better TTP or achievement of TE4 at univariate analysis were entered into the multivariate regression model. A two-tailed P-value of <0.05 was considered as statistically significant.

Results

Characteristics of the Patients and HCCs

Total 35 HCC patients were treated with B-TACE between June 2013 and August 2016. 24 patients were treated with c-TACE before B-TACE. 11 patients were naïve case for TACE procedures. The date of the last follow-up evaluation was March 2017. The characteristics of the treated patients and tumor are summarized in Table 1. Median tumor size was 21 mm (12.25-65). Each 21 and 14 patient had <3 and $\geqq 4$ in number of nodules. Among 35 patients, each 15/11/9 was categorized to Barcelona Clinic Liver cancer (BCLC) staging A/B/C. According to the TNM staging

of the Liver Cancer Study Group of Japan, 8.6% was stage I, 40% stage II and 51.4% stage III. In the patients, 40 nodules have been treated by B-TACE and these nodules were assessed as the targeted nodules. Among the 40 targeted nodules, 25 nodules were treated by epirubicin and the rest 15 was miriplatin.

Overall survival and response rate of B-TACE

OS of the patients treated with B-TACE was 26.4 months (Figure 1A). And one-, two-, three-year survival rate of the patients was each 85.4%, 52.3% and 29.9%. The radiological effects of B-TACE in the targeted lesions were shown in Figure 1B and 1C. 21 cases (52.5%) showed TE4, 6 (15%) was TE3, 10 (25%) was TE2 and 3 (7.5%) was TE1 (Figure 1B). Namely, local RR of B-TACE was 67.5% and local DCR of B-TACE was 92.5%. The local TTP in the targeted lesions treated with B-TACE was 8.1 months (Figure 1C).

Safety assessment of B-TACE

We have assessed the AEs of B-TACE categorized to “over grade 3”. 10 patients showed elevation of transaminase and one patient was liver dysfunction. And 1 patient suffered obstructive cholangitis due to tumor collapse after tumor

necrosis caused by B-TACE. All patients suffered from over grade 3 AEs have been improved by conservative treatments.

Assessment of the factors associated with better local TTP in B-TACE

We have analyzed the factors associated with better TTP of B-TACE to clarify which factors are the most important to achieve better TTP of B-TACE. Univariate and multivariate analyses were shown on Table 2. Univariate analysis was performed by the followed factors, age (≧65/ <65 years old), gendar (Male/ Female), Child-Pugh class (A/ B), tumor size (2</ 2≧; cm), the effects of B-TACE (TE4/ TE1,2 and 3), TACE history (naïve/ previous history). Among these factors, the effects of B-TACE (TE4, $p<0.0001$), TACE history (naïve case, $p=0.0418$) were significant factors associated with local TTP in univariate analysis. Next, multivariate analysis was performed using these factors. Notably, the effects of B-TACE (TE4, $p=0.0338$: HR 15.99) and TACE naïve case ($p=0.0304$: HR 3.62) were independent significant factors which associated with better TTP of B-TACE.

Assessment of the factors associated with achievement of TE4 in B-TACE

TE4 was the most significant factor which associated with better TTP of the

targeted lesions treated with B-TACE. Thereby, we have analyzed which factors associated to achieve TE4 by B-TACE. Univariate and multivariate analyses were shown on Table 3. Univariate analysis was performed by the followed factors, age (≧65/ <65 years old), gendar (Male/ Female), Child-Pugh class (A/ B), tumor size (2</ 2≧; cm), regimens (Epirubicin/ Miriplatin), TACE history (naïve/ previous TACE history). Among these factors, TACE naïve case (p=0.0149) was a significant factor associated with achievement of TE4 in univariate analysis. Next, multivariate analysis was performed using these factors in addition to the regimens (Epirubicin, p=0.0601). Notably, both regimens (Epirubicin, p=0.0088) and TACE naïve case (p=0.0072) were independent significant factors which associated with achievement of TE4 by B-TACE.

Difference of RR between epirubicin and miriplatin in B-TACE

To achieve TE4 by B-TACE, epirubicin was more effective than miriplatin as the regimen which was used in B-TACE procedures. TE4 rate of each regimen, i.e. epirubicin and miriplatin, was 64% (16/ 25 nodules) and 33% (5/ 15 nodules). Epirubicin showed a positive tendency in TE4 rate, compared with miriplatin (p=0.058, Figure 2A). Local TTP curve associated with the regimens has been

assessed (Figure 2B). Epirubicin showed longer local TTP of the targeted lesions compared with miriplatin with a positive tendency (Epirubicin 15.1 months, Miriplatin 4.4 months; p=0.056)

Discussion

In this study, we have assessed the therapeutic effects and safety of B-TACE as a single center retrospective study. With respect to the therapeutic effects of B-TACE, local TE4 ratio was 52.5% and local TTP was 8.1 months. Achievement of TE4 on the targeted lesions significantly prolonged local TTP. Univariate and multivariate analyses showed that use of epirubicin and TACE naïve case were significantly associated with achievement of TE4.

In c-TACE procedures, miriplatin seems not to recommend as a first choice of anti-cancer agent according to several reports [17, 21]. Miyayama et al. has reported that local control rate of miriplatin is inferior to that of other agents. Viscosity of miriplatin is higher than the others, which results in lower local control for the treated lesions[14]. However, miriplatin is often used as an anticancer agent on B-TACE in several previous reports because balloon occlusion can push miriplatin into tumor feeding artery with high pressure[9, 15, 16]. Therefore, they recommend the

use of miriplatin on B-TACE. However, according to the results of this study, TE4 rate of epirubicin and miriplatin was each 64% and 33%. And each median TTP was each 15.1 and 4.4 months. Taken together, these results suggest that epirubicin is more optimal drug for B-TACE than miriplatin. Of course, the number of patients assessed in this study is still not enough to conclude the result. Therefore, further accumulation of clinical experience is needed to increase the evidence which drug is a suitable drug for B-TACE procedures.

The amount of the injected chemotherapeutic drugs with lipiodol or jelpart on B-TACE are increased compared with those on c-TACE because the drugs are able to be forced into nodules without back flow by balloon occlusion. Maruyama et al. has also reported that amount of the injected lipiodol has increased in B-TACE, compared with c-TACE[22]. Several studies describe that RR of B-TACE was significantly higher than that of c-TACE[12, 15]. This could be double-edged sword. Stronger embolic effect and increase of the injected chemotherapeutic drugs could induce severe AEs or complications. Actually, Maruyama et al. has also reported the incidence of severe biliary injury has increased on B-TACE, compared with c-TACE[22]. While there were no significant differences in incidence of the other AEs regarding with post TACE syndrome. Also according to the Arai et al' report, the

incidence of AEs in B-TACE was not increase compared with that in c-TACE[23]. In the present study, several 'over grade 3' AEs have appeared after B-TACE. However, all AEs appeared after B-TACE were manageable by conservative treatments. In summary regarding with AEs of B-TACE, it is thought that B-TACE is safe and acceptable procedure, if the procedures and management have been precisely performed.

Despite this study showed an important finding regarding with the drug that should be selected on B-TACE, it still has several limitations. The study size is limited and this study is a single center retrospective study. And, we finally need to compare the overall effects between c-TACE and B-TACE. To solve these limitations, we should conduct a prospective double arm study of c-TACE and B-TACE. However, the most important thing might not be comparison of the effect of each TACE. The most important thing is whether how much multidisciplinary approach using each TACE, i.e. c-TACE, B-TACE and drug-eruting beads TACE[24] can contribute to prolongation of overall prognosis of the intermediate HCC patients.

In conclusion, epirubicin was more effective than miriplatin as the anticancer drug used in B-TACE in TE4 rate and local TTP of the targeted lesions. However, further accumulation of practical experience and clinical evidence are

necessary to clarify the efficacy of B-TACE in treatment of HCC.

Acknowledgement

The authors have no conflict of interests.

References

[1] Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology*. 1983; **148**: 397-401.

[2] Forner A, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2014; **11**: 525-35.

[3] Kudo M, Matsui O, Izumi N*, et al.* JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver Cancer*. 2014; **3**: 458-68.

[4] Sangiovanni A, Colombo M. Treatment of hepatocellular carcinoma: beyond international guidelines. *Liver Int*. 2016; **36 Suppl 1**: 124-9.

[5] Aramaki T, Moriguchi M, Bekku E, Asakura K, Sawada A, Endo M. Comparison of epirubicin hydrochloride and miriplatin hydrate as anticancer agents for transcatheter arterial chemoembolization of hepatocellular carcinoma. *Hepatol Res*. 2013; **43**: 475-80.

[6] Kawamura Y, Ikeda K, Hirakawa M*, et al.* Efficacy of platinum analogue for advanced hepatocellular carcinoma unresponsive to transcatheter arterial chemoembolization with epirubicin. *Hepatol Res*. 2009; **39**: 346-54.

[7] Brown DB, Pilgram TK, Darcy MD*, et al.* Hepatic arterial chemoembolization for hepatocellular carcinoma: comparison of survival rates with different embolic agents. *J Vasc Interv Radiol*. 2005; **16**: 1661-6.

[8] Horikawa M, Miyayama S, Irie T, Kaji T, Arai Y. Development of Conventional Transarterial Chemoembolization for Hepatocellular Carcinomas in Japan: Historical, Strategic, and Technical Review. *AJR Am J Roentgenol*. 2015; **205**: 764-73.

[9] Asayama Y, Nishie A, Ishigami K*, et al.* Hemodynamic changes under balloon occlusion of hepatic artery: predictor of the short-term therapeutic effect of balloon-occluded transcatheter arterial chemolipiodolization using miriplatin for hepatocellular carcinoma. *Springerplus*. 2016; **5**: 157.

[10] Minami Y, Minami T, Chishina H*, et al.* Balloon-Occluded Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma: A Single-Center Experience. *Oncology*. 2015; **89 Suppl 2**: 27-32.

[11] Matsumoto T, Endo J, Hashida K*, et al.* Balloon-occluded arterial stump pressure before balloon-occluded transarterial chemoembolization. *Minim Invasive Ther Allied Technol*. 2016; **25**: 22-8.

[12] Irie T, Kuramochi M, Kamoshida T, Takahashi N. Selective balloon-occluded transarterial chemoembolization for patients with one or two hepatocellular carcinoma nodules: Retrospective comparison with conventional super-selective TACE. *Hepatol Res*. 2016; **46**: 209-14.

[13] Kora S, Urakawa H, Mitsufuji T*, et al.* Warming effect on miriplatin-lipiodol suspension for potential use as a chemotherapeutic agent for transarterial chemoembolization of hepatocellular carcinoma: In vitro study. *Hepatol Res*. 2013; **43**: 1100-4.

[14] Ikeda K, Kawamura Y, Kobayashi M*, et al.* Beneficial effect of arterial embolization with warmed miriplatin for multiple hepatocellular carcinoma.

Hepatol Res. 2016.

[15] Kawamura Y, Ikeda K, Fujiyama S*, et al.* Usefulness and limitations of balloon-occluded transcatheter arterial chemoembolization using miriplatin for patients with four or fewer hepatocellular carcinoma nodules. *Hepatol Res*. 2017; **47**: 338-46.

[16] Ogawa M, Takayasu K, Hirayama M*, et al.* Efficacy of a microballoon catheter in transarterial chemoembolization of hepatocellular carcinoma using miriplatin, a lipophilic anticancer drug: Short-term results. *Hepatol Res*. 2016; **46**: E60-9.

[17] Miyayama S, Yamashiro M, Shibata Y*, et al.* Comparison of local control effects of superselective transcatheter arterial chemoembolization using epirubicin plus mitomycin C and miriplatin for hepatocellular carcinoma. *Jpn J Radiol*. 2012; **30**: 263-70.

[18] Otsuji K, Takai K, Nishigaki Y*, et al.* Efficacy and safety of cisplatin versus miriplatin in transcatheter arterial chemoembolization and transarterial infusion chemotherapy for hepatocellular carcinoma: A randomized controlled trial. *Hepatol Res*. 2015; **45**: 514-22.

[19] Kudo M, Ueshima K, Kubo S*, et al.* Response Evaluation Criteria in Cancer of the Liver (RECICL) (2015 Revised version). *Hepatol Res*. 2016; **46**: 3-9.

[20] Kudo M, Kubo S, Takayasu K*, et al.* Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 Revised Version). *Hepatol Res*. 2010; **40**: 686-92.

[21] Hashimoto N, Iwazawa J, Ohue S, Mitani T. Effect of transarterial chemoembolization with miriplatin plus epirubicin on local control of hepatocellular

carcinoma: a retrospective comparison with miriplatin monotherapy. *Onco Targets Ther*. 2013; **6**: 1025-30.

[22] Maruyama M, Yoshizako T, Nakamura T, Nakamura M, Yoshida R, Kitagaki H. Initial Experience with Balloon-Occluded Trans-catheter Arterial Chemoembolization (B-TACE) for Hepatocellular Carcinoma. *Cardiovasc Intervent Radiol*. 2016; **39**: 359-66.

[23] Arai H, Abe T, Takayama H*, et al.* Safety and efficacy of balloon-occluded transcatheter arterial chemoembolization using miriplatin for hepatocellular carcinoma. *Hepatol Res*. 2015; **45**: 663-6.

[24] Hui Y, Ruihua T, Jing L*, et al.* Meta-Analysis of Doxorubicin-Eluting Beads via Transcatheter Arterial Chemoembolization in the Treatment of Unresectable Hepatocellular Carcinoma. *Hepatogastroenterology*. 2015; **62**: 1002-6.

Figure Legends

Figure 1

A. Overall survival curve of 35 HCC patients received B-TACE. MST was 26.4 months.

B. The radiological effects of B-TACE in the targeted lesions are shown. 21 cases (52.5%) showed TE4, 6 (15%) was TE3, 10 (25%) was TE2 and 3 (7.5%) was TE1. Local responase rate (RR) of B-TACE was 67.5% and local disease control rate (DCR) of B-TACE was 92.5%.

C. The time to pregression curve of the targeted lesions treated with B-TACE are shown. The local TTP in the targeted lesions treated with B-TACE was 8.1 months.

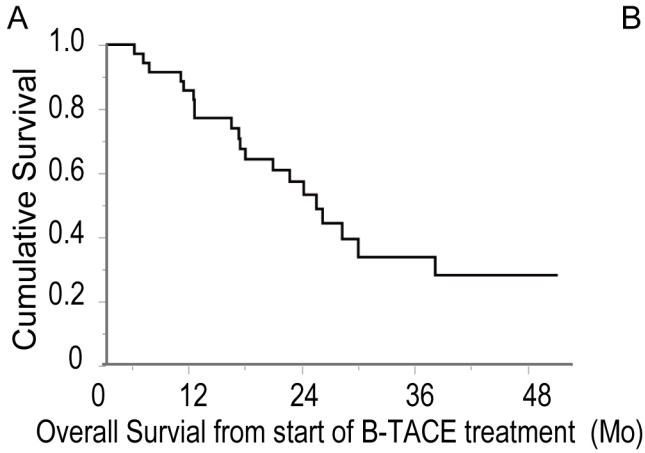
Figure 2

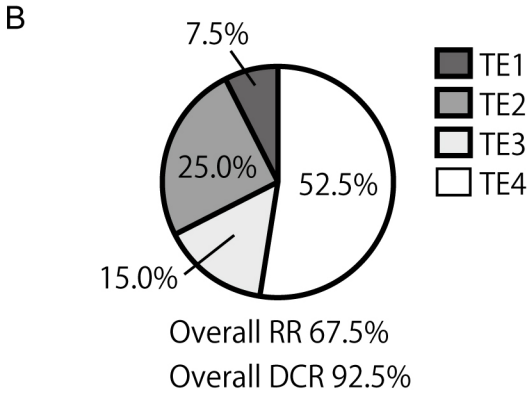
A. Local therapeutic response rate (RR) of B-TACE using epirubicin and miriplatin. Each RR of epirubicin and miriplatin, was 64% (16/ 25 nodules) and 33% (5/ 15 nodules, p=0.058.

B. Local time to progression (TTP) curve of B-TACE using epirucin and miriplatin. associated TTP of B-TACE using epirubicin and miriplatin was 15.1 and 4.4

months, respectively (p=0.056)

Figure 1


A
1.0
0.8
0.6
0.4
0.2
0
Cumulative Survival
0
12
24
36
48
Overall Survial from start of B-TACE treatment (Mo)


B
7.5%
25.0%
52.5%
15.0%
TE1
TE2
TE3
TE4
Overall RR 67.5%
Overall DCR 92.5%

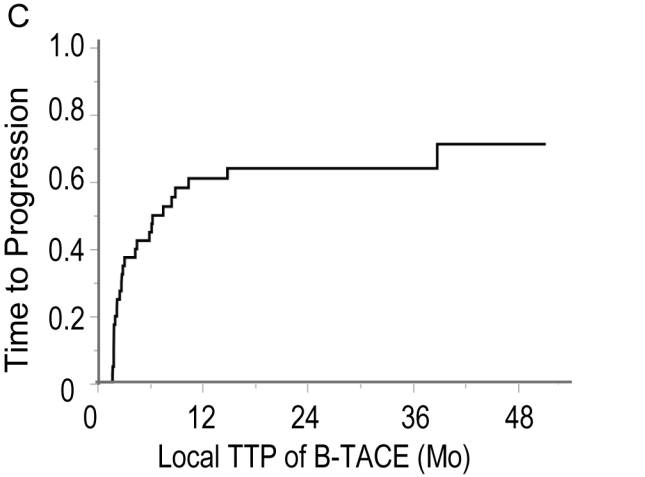
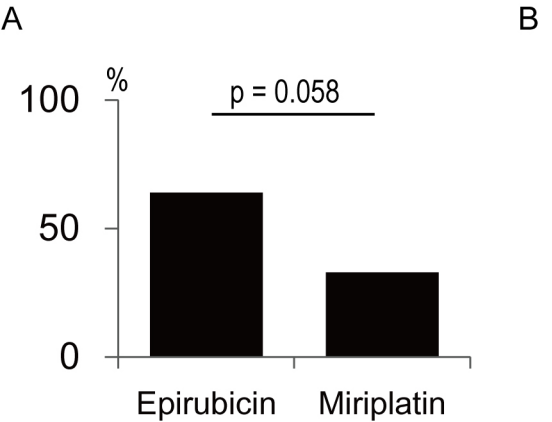

C
1.0
0.8
0.6
0.4
0.2
0
Time to Progression
0
12
24
36
48
Local TTP of B-TACE (Mo)

Figure 2


A
%
100
50
0
p = 0.058
Epirubicin
Miriplatin
Response Rate of B-TACE in eahc regimen

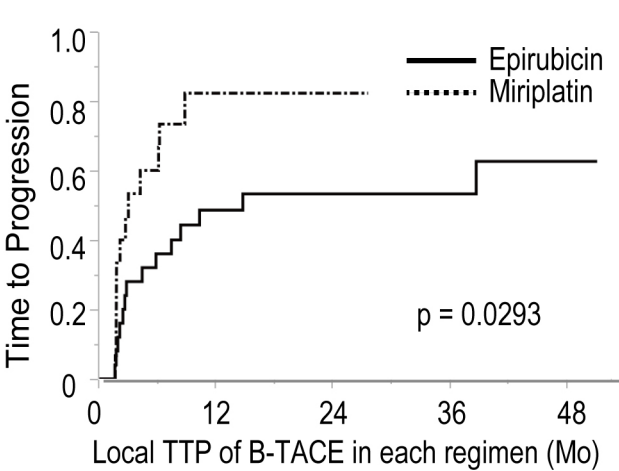

B
Time to Progression
1.0
0.8
0.6
0.4
0.2
0
Epirubicin
Miriplatin
p = 0.0293
0
12
24
36
48
Local TTP of B-TACE in each regimen (Mo)

Table 1 Baseline clinical and tumor characteristics of the patients

Clinical characteristics of 35 patients	Total (n=35)	Epriubicin (n=24)	Miriplatin (n=11)	P-value
Age (years)	73 (61-85)	72 (61–84)	75 (62–85)	0.1169
Gendar				
Male / Female	66 / 14	14 / 10	8 / 3	0.4133
Etiology				
HBV	1 /34	0 / 24	1 / 10	0.134
HCV	22 / 13	18 / 6	4 / 7	0.0281
Child-Pugh class				
A / B / C	23 / 12 / 0	14 / 10 / 0	9 / 2 / 0	0.1742
Tumor characteristics				
BCLC stage				
A / B / C	15 / 11 / 9	11 / 8/ 5	4 / 3 / 4	0.6208
Tumor size (mm)	21 (12.25-65)	21 (13.75-65)	18.6 (12.25-45)	0.1578
Number of tumor localized segments < 2 / ≧3	18 / 17	13 / 11	5 / 6	0.6321
Number of tumor nodules				
≦3 / 4<	21 / 14	14 / 10	7 / 4	0.7662
AFP* (ng/ml)	11.1 (1.9-9851)	8.35 (1.7-1769)	11.4 (3.9-9851)	0.3112
DCP** (mAU/ml)	67 (10-278523)	65 (10-278523)	121 (30-8245)	0.6321

* Alphaphetoprotein, ** Des-gamma carboxyprothrombin

Table 2 Univariate and multivariate analyses for the factors which influence better local time to progression

Variable	Univariate analysis (P-value)	Multivariate analysis (P-value)	Hazard Ratio (95% CI)
Age	0.1502		
＜ 65 years			
≧ 65 years			
Gendar	0.1525		
Male			
Female			
Child-Pugh class	0.8612		
A			
B			
BCLC stage A / B / C	0.3454		
Tumor size ≦2 / > 3	0.7870		
Number of tumor localized segments	0.3254		
>3 / ≦2			
Previous TACE history	0.1053		
+ / -			
Number of tumor nodules	0.0649		
≧4 / < 3			
AFP level	0.0034	0.7158	
≦200 ng/ml / > 200 ng/ml			
Regimen	0.1148		
Epirubicin / Miriplatin			
Therapeutic effect	< .0001	< .0001	
TE4 / TE3, 2, 1*			20.56 (4.60-148.2)
TE3, 2, 1 / TE4			0.0421 (0.006-0.21)

*; RECICL criteria, TE4 100% necrosis, TE3 50-100% necrosis, TE2 between TE3 and TE1, TE1 tumor enlargement more than 25%

Table 3 Univariate and multivariate analyses for the factors which achieve TE4 in B-TACE

Variable	Univariate analysis (P-value)	Multivariate analysis (P-value)	Hazard Ratio (95% CI)
Age	0.2526		
Gendar	0.6312		
Child-Pugh class A B	0.5542		
BCLC stage A / B / C	0.0540	0.0556	
Tumor size <2 / 3≦	0.7960		
AFP level ≦200 ng/ml / > 200 ng/ml / > 200 ng/ml / ≦200 ng/ml	0.0739	0.0083	 0.0066 (2.37×10^{-5}-1.87) 149.8 (0.53-42069.9)
Number of tumor localized segments >3 / ≦2	0.0613	0.4569	
Number of tumor nodules ≧4 / < 3	0.0253	0.9429	
Previous treatment history + / - - / +	0.0179	0.0010	 0.014 (0.0005-0.37) 70.12 (2.65-1850.6)
Regimen Epirubicin / Miriplatin Miriplatin / Epirubicin	0.0583	0.0058	 31.35 (1.43-684.6) 0.031 (0.0014-0.69)