Original Article

Chemoembolization Dosage and Tumor Burden: A Predictive of Post-TACE Fever in Hepatocellular Carcinoma Patients

Thanacharoenkit R[1]
Keratikhun Y[2]
Boonsirichan R[1]

ABSTRACT

Background: Fever is common sequelae after transcatheter arterial chemoembolization (TACE). Although there are studies showing that the a tumor necrosis is the main cause of post-TACE fever, the actual causes of fever is an individual patient often raises concerns by the attending physician, leading to extensive septic work-up and initiation of antibiotic treatment. The aim of this study was to assess the causes of and the factors predicting fever after TACE.

Methods: Twenty-one patients with inoperable HCC underwent 40 sessions of TACE treatment. Data was collected and analyzed on demographic patterns, potential predictive factors for post TACE fever, correlations between post-TACE fever and chemoembolization dosage or tumor size, and incidence of post-procedural infection.

Results: Post-TACE fever occurred in 85% of the study population, with the mean duration of 3 ± 2.4 day. The mean tumor size was 6.1 ± 4.2 cm, the mean chemoembolization dosage 46 ± 13 mg/mL, and 42% considered as effective treatment by revised RECIST criteria. Usage of gelfoam embolization (OR16, 95%CI 1.87-136.70, $p = 0.011$), a larger tumor size (8.0 ± 4.7 vs. 4.4 ± 1.4 cm, $p = 0.001$) and a higher total dose delivery of chemoembolizing agents (47 vs. 38 mg/mL, $p = 0.002$) were the predictive factors of post-TACE fever. Tumor volume, chemoembolizing dosage, and elevation of serum AST, ALT after TACE appeared to correlate with the duration of fever ($p < 0.007$, 0.056, 0.022, 0.034 respectively) but not so strongly (r = 0.457, 0.331, 0.456, 0.417 respectively). No evidence of infection was found in any study patient, and no useful of pre-TACE biochemistry test can predict the occurrence of post-TACE fever in this study.

Conclusion: Fever after TACE was common. The predictive factors of post-TACE fever were the usage of gel foam embolization, higher chemoembolization dosage and larger tumor size. Infectious complications were not observed.

Key words : Post-TACE fever, chemoembolization, hepatocellular carcinoma

[Thai J Gastroenterol 2012; 13(2): 104-112.]

[1]*Division of Gastroenterology, Department of Internal Medicine,* [2]*Division of Radiointervention, Department of Radiology, Vajira Hospital, Bangkok, Thailand.*

Address for Correspondence: *Rattana Boonsirichan, M.D., Division of Gastroenterology, Department of Internal Medicine, Vajira Hospital, Bangkok, Thailand.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common cancer and a major disease burden worldwide, especially so in South-East Asia and Africa[1]. Because of high prevalence of chronic hepatitis B and chronic hepatitis C infection in Thailand[2,3], the incidence of hepatocellular carcinoma was around 30-40 persons per 100,000 male population[4]. Hepatocellular carcinoma is often asymptomatic, and advanced disease at the time of diagnosis makes curative treatment feasible in only 20% of patients[5,6].

Transcatheter arterial chemoembolization (TACE) was approved as a palliative treatment modality in most accepted standard guidelines, such as the "Barcelona clinic liver cancer staging classification and treatment[20] (Figure 1).

TACE inevitably results in hypoxic tumor necrosis, hence the common post-TACE side effects especially fever. The prevalence of post-TACE fever ranges from 18 to 74% in previous studies[7,15-18,21,22]. Other side effects include nausea and vomiting, pain, bleeding, local infection and systemic infection. Serious side effects such as hepatic failure, renal failure, and tumor lysis syndrome are rare[8-14]. In a study in which the surgically resected livers of HCC patients previously undergoing TACE were examined, post-TACE fever was related not only to tumor necrosis, but also to non-tumorous liver cell damage[19]. Whatever the cause of fever, patients feel uncomfortable and physicians feel anxious and concerned. Thus factors that may predict the occurrence of post-TACE fever would be useful for clinical management, and may reduce the extensive septic work up as well as the length of hospital stay. The aim of this study was to assess the causes of and the factors that may predict post-TACE fever.

MATERIAL AND METHODS

Patients

Between January 2010 and December 2010, 21 consecutive patients with inoperable HCC who underwent 40 TACE sessions at the Department of Medicine, Vajira Hospital, Bangkok Metropolitan Administration University, were recruited for study. The selection criteria in this study were the same as those for TACE, namely:

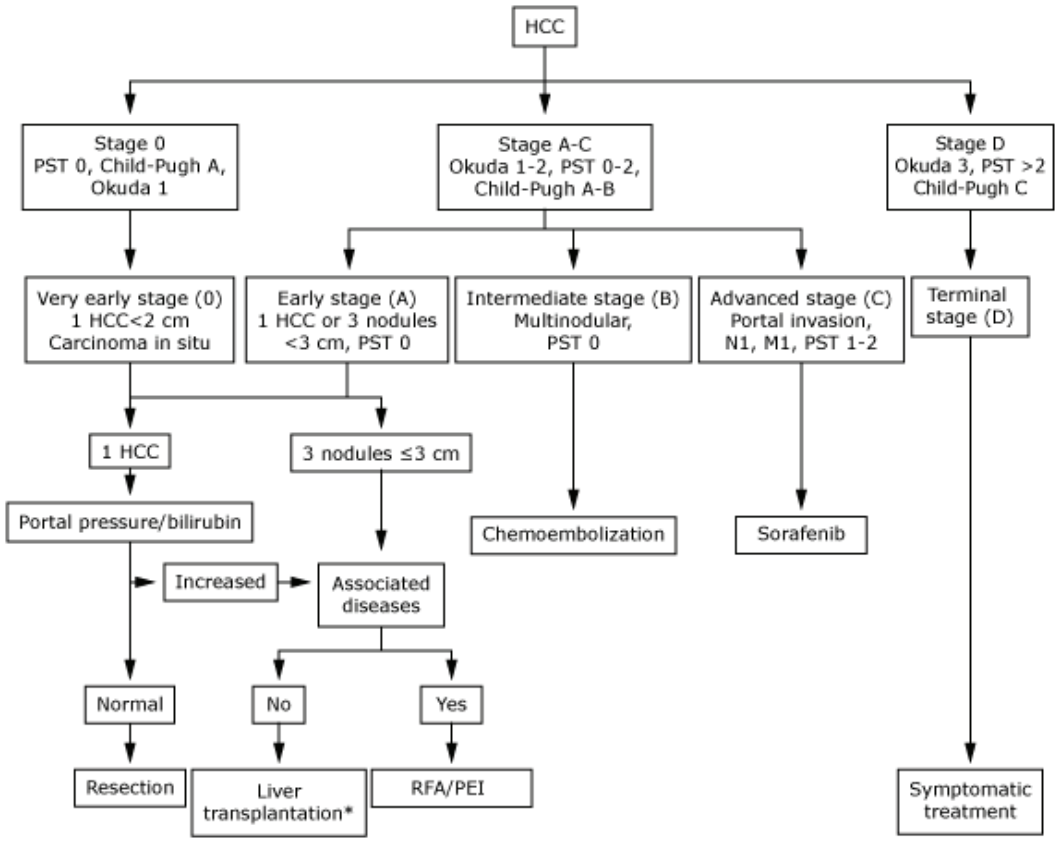

Figure 1. Barcelona Clinic Liver Cancer Staging classification and treatment.

- Adults aged over 18
- HCC diagnosed from histology, or from underlying cirrhosis or chronic viral hepatitis with a hypervascular mass from 2 imaging studies (CT and MRI) or from 1 imaging study plus serum α fetoprotein more than 200 ng/mL
- appropriate indication for TACE including inoperable HCC or unsuitability for liver transplantation according to Barcelona guideline
- patient's agreement for a written consent.

Contraindication for TACE included

- thrombosis of the main portal vein, hepatic encephalopathy, biliary obstruction, extrahepatic metastasis, Child-Pugh class C
- tumor burden >50% of the liver
- cardiac or renal insufficiency (serum creatinine > 1.5 mg/dL).

Procedure

TACE was performed with standard aseptic technique. After super-selection of the tumor feeding artery, doxorubicin ± mitomycin mixed with Lipiodol was infused, the dosage based on tumor size and vascularity assessment. This was followed with a permanent occluding agent such as gelfoam (gelatin sponge). Data was collected on the cumulative dosage of each chemo-agents and the usage of gelfoam embolization. The total dosage delivered (TDD) of TACE was calculated from dosage of doxorubicin (mg) + dosage of mitomycin (mg) + dosage of Lipiodol (mL).

Physical examination, chest X-ray, complete blood count, serum biochemistries, hepatitis B surface antigen, anti-HCV and serum AFP were performed prospectively in each patient. Tumor characteristics such as size and location were assessed on the basis of imaging findings. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP) and white blood cell count (WBC) were monitored at the day of fever onset, day-2 and day-5 after TACE procedure whether the patient had fever or not. Septic work up was carried out if the patient developed post-TACE fever (Figure 2).

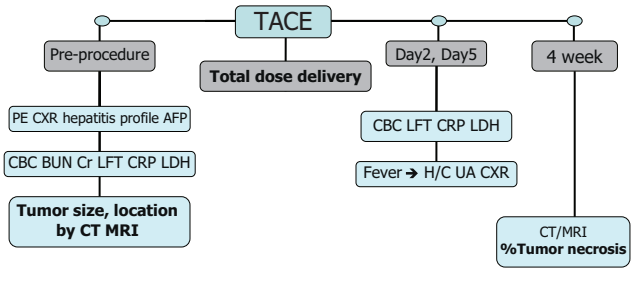

Figure 2. Method and data collection.

Efficacy of TACE

The size of tumor was assessed by dynamic computed tomography (CT) which was filmed within one month before procedure and at one month post procedure in each section. The effects of TACE on the tumors were determined in two ways firstly by the tumor size in one dimension, with combined widest diameter(s) of the tumor mass(es), and secondly by in three dimensional volume calculated from CT findings. The efficacy of TACE was then categorized with reference to the revised RECIST[24] criteria as follow:

- complete response : disappearance of all measurable disease,
- partial response : a reduction of 30% in tumor burden from baseline,
- stable disease : between partial response and progressive disease,
- progressive disease : at least 20% increase in tumor burden from baseline.

Effective cases were defined as complete or partial response, while ineffective cases were defined as stable or progressive disease.

Monitoring and management of post-TACE fever

Post-TACE fever was defined as body temperature equal or more than 38˚C by oral route. No pre- and post-procedural prophylactic antibiotic and antipyretics were prescribed when high temperature was fist observed. Bacterial hemoculture, urine analysis with culture, and chest X-ray were performed in patients who developed fever after TACE. Empiric broad-spectrum intravenous antibiotics were chosen in cases with evidence of an infection.

Statistical analysis

As each patient could undergo more than one treatment sessions, the analysis was based on the number of TACE sessions. Results were expressed as mean values ± the standard error of the mean. Chi-square test and Fisher exact test were used for comparison of categorical variables. Mann-Whitney U- test was used to analyze continuous variables between groups. Pearson's correlation co-efficient was used to deter-

mine the relationship between numerical variables, such as the dose of chemoembolization and the duration of fever. To determine the risk factors associated with post-treatment fever, patient and tumor-related variables including age, gender, underlying hepatitis, underlying illnesses, Child-Pugh class, size of tumor, amount of chemo-embolization agents used in TACE, and serum biochemistries were included for analysis. Statistical analyses were performed using the SPSS software SPSS16.0. Results were considered statistically significant at $p < 0.05$.

RESULTS

Patient characteristics

The characteristics of 21 patients who underwent 40 TACE sessions are listed in Table 1. Each patient received 1 to 4 treatment sessions (mean 2.45). The mean age was 57 years, with male predominance. A common etiology was hepatitis C viral infection. Liver cirrhosis was noted in 95% of patients, mostly Child-Pugh class A. Pre-procedure serum biochemistries were within normal range, except for elevated baseline AST, ALT and LDH levels. Diagnostic values of serum AFP for HCC >200 ng/mL were found in only 17.5% of the study population. The mean total dose delivery was 46 ± 13 mg/mL (range 20-80 mg).

Tumor profiles and response after TACE

About half of the patients had multiple tumors, ranging from 2 to 5 lesions. The mean tumor size was 6.0 ± 4.2 cm (range1-25 cm), calculated from combined widest diameters of all mass(es) in each patient, excepting unmeasurable tiny liver nodules. Tumor volume was calculated from three dimensional measurements (wide*long*thickness), the mean tumor volume being 518 ± 1,577 cm^3 (range 5-9900). The percentages of residual tumor at four weeks, calculated from the relative volume of preexisting tumor plus the volume(s) of new lesion(s) was 110 ± 102% cm^3 (range 28-609%).

We categorized tumor response by the difference between the percentages of tumor volume pre-procedure and at one month post-procedure including new lesion(s). Seven patients had only a single TACE treatment; 4 patients were lost to follow up, and 3 patients still had the next appointment for TACE after the end of study, thus only 33 TACE sessions were re-evaluated with a CT scan. Effective cases by the revised

Table 1. Demographic data of HCC patients receiving TACE (n = 40 sessions).

Mean age (years, range)	57 (29-79)
Gender (M/F)	39/1
Etiology (n,%)	
Positive HBsAg	7 (17.5)
Positive anti-HCV	25 (62.5)
Alcohol	8 (20)
Underlying (n,%)	
Cirrhosis	38 (95)
Child-Pugh A/B	31/9 (77.5/22.5)
DM	13 (32.5)
Renal insufficiency	4 (10)
HIV infection	0
Blood biochemistry	
Albumin (g/dL)	3.1 ± 0.4
Creatinine (mg/dL)	1 ± 0.2
Total bilirubin (mg/dL)	1.2 ± 0.6
AST (U/L)	108 ± 150
ALT (U/L)	60 ± 34
LDH (U/L)	523 ± 178
C-reactive protein (mg/dL)	22 ± 21
Platelet (/mL)	150,725 ± 86,183
Prothrombin time (s)	14 ± 1.4
Serum AFP >200ng/mL	7 (17.5)
Chemoembolization	
Dose of doxorubicin (mg) (n = 38)	35 ± 11
Dose of mitomycin (mg) (n = 8)	14 ± 5.5
Dose of Lipiodol (mL) (n = 39)	9.5 ± 1.84
Total dose delivery (range)	6 ± 13 (20-80)
Gelfoam used (n,%)	35 (87.5)
Tumor profile	
Tumor number : solitary/multiple	19/21 (range 1-5)
Tumor size (cm)	6.0 ± 4.2 (range 1-25)
Tumor volume (cm^3)	518 ± 1,577 (range 5-9900)
Involve main portal vein (n,%)	6 (15%)
% tumor remain at 4 wk (cm^3)	110 ± 102 (range 28-609)

Table 2. Efficacy of treatment and hospital course.

Tumor response (RECIST) (n,%)	
Complete response	2 (6%)
Partial response	12 (36%)
Stable case	15 (46%)
Progressive disease	4 (12%)
Single TACE (n)	7
Hospital course / side effect (n = 40)	
Fever	34 (85%)
Fever (days, range)	3 ± 2.4 (1-9)
Hospital length (days, range)	6 (2-12)
Abdominal pain	12 (30%)

Table 3. Comparison of TACE sessions with and without post-treatment fever.

	With fever (n = 34)	Without fever (n = 6)	*p*-value*
Age (mean ± SD), (yrs)	56.3 ± 13	61.2 ± 11	0.397
Hospital length (days)	6.4	3.5	0.014
Underlying diseases (n,%)			
Cirrhosis	32 (94%)	6 (100%)	1.000
Child-Pugh A	27 (79%)	6 (100%)	0.567
B	7 (21%)	0	
Diabetes Mellitus	10 (29%)	3 (50%)	0.370
Renal insufficiency	4 (12%)	0	1.000
Hepatitis status (n,%)			
Hepatitis B	7 (21%)	0	0.567
Hepatitis C	19 (56%)	6 (100%)	0.067
Blood biochemistry before TACE			
White blood cell (cells/mL)	6,263	5,483	0.580
Platelet (cells/mL)	156,000	119,000	0.340
AST (U/L)	109	110	0.987
ALT (U/L)	55	96	0.006
Total bilirubin (mg/dL)	1.17	1.45	0.298
Albumin (g/dL)	3.10	3.15	0.839
LDH (U/L)	542	450	0.298
C-reactive protein (mg/dL)	22.40	15.67	0.503
AFP (ng/mL)	5,091	69	0.491
Blood biochemistry after TACE			
White blood cell (cells/mL)	7,736	9,550	0.275
Platelet (cells/mL)	136,000	127,000	0.798
AST (U/L)	250	98	0.003
ALT (U/L)	119	102	0.425
Total bilirubin (mg/dL)	1.91	1.65	0.513
Albumin (g/dL)	2.82	3.36	0.039
LDH (U/L)	1181	531	0.293
C-reactive protein (mg/dL)	96.31	24.75	0.375
Tumor profile			
Tumor size (cm)	8 ± 4.7	4.4 ± 1.4	0.001
Tumor volume (cm^3)	601	45	0.433
Portal vein involve	6 (18%)	0	0.565
% tumor remain at 4 wk (cm^3)	114	87	0.634
Chemoembolization dosage			
Dose of doxorubicin (mg)	36	28	0.006
Dose of mitomycin (mg)	3.16	0	0.006
Dose of Lipiodol (mL)	9.23	9.67	0.680
Total delivery dose	47	38	0.002
Gelfoam embolization	32 (94%)	3 (50%)	0.018
Tumor response (RECIST) (n = 33)			
Complete response	1	1	0.202
Partial response	11	1	
Stable case	4	0	
Progression	13	2	

RECIST criteria were 42% (6% complete response, 36% partial response). Septic profiles (hemoculture, urinalysis and chest X-ray) were negative, as shown in Table 2.

Fever after TACE and clinical features

Thirty-four TACE episodes (85%) were associated with fever that almost always occurred within the first two days after TACE. Such post-TACE fever was usually self-limiting, lasting from 1 to 9 days. The average length of hospital stay was 6 days. Patients were discharged after resolution of fever and after negative septic profiles. Infective occurrences were not identified in this study. A comparison of TACE sessions with and without fever is shown in Table 3. Patients in the fever group were younger, their average hospital stay significant longer, with significantly greater AST elevation and lower albumin level after TACE. Additionally, serum ALT, LDH and CRP levels tend to rise higher in the fever group. The tumor size was significantly larger in the fever group (8 ± 4.7 vs. 4.4 ± 1.4 cm, $p = 0.001$), and a similar trend was observed for tumor volume but without statistical significance. Significantly higher dosages of doxorubicin and mitomycin as well as higher total dose delivery (doxorubicin ± mitomycin ± lipiodol) were observed in the fever group (TDD 47 vs. 38 mg/mL, $p = 0.002$). Use of gelfoam embolization was associated with a significantly higher incidence of fever (94% vs. 50%, $p = 0.018$). The second most common side effect was mild right upper quadrant pain that was seen in 30% of all TACE procedures.

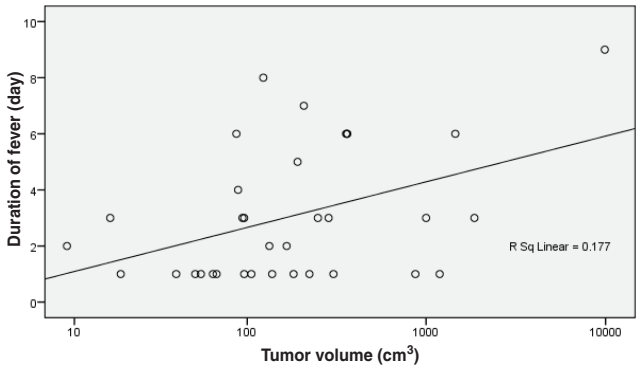

Figure 3. Correlations between fever duration and tumor volume (n = 34, r = 0.457, $p = 0.007$).

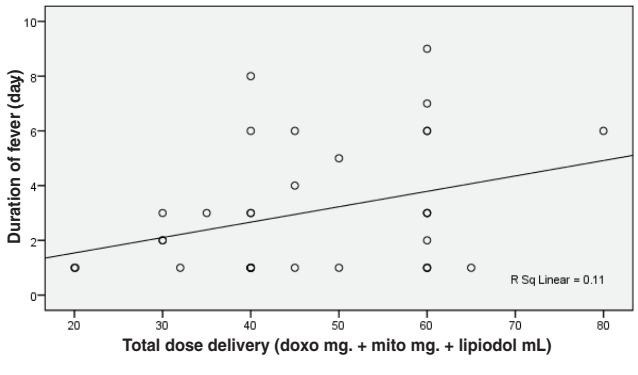

Figure 4. Correlations between duration of fever and cumulative chemoembolization dosage (n = 34, r = 0.331, $p = 0.056$).

Correlation with the duration of fever

Figures 3-6 shown correlations between the duration of fever and the tumor volume (r = 0.457, p =

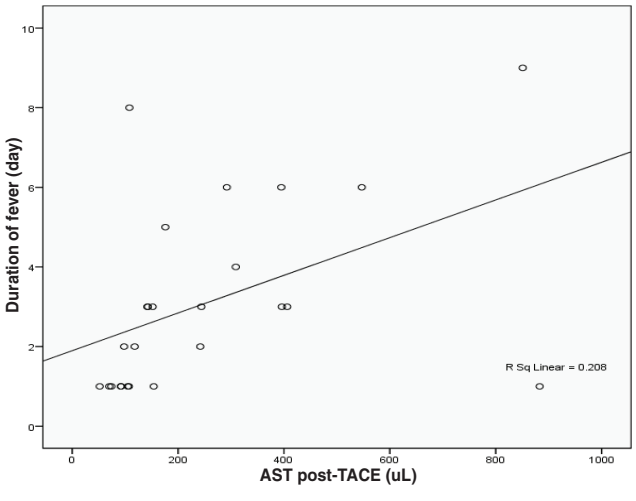

Figure 5. Correlations between duration of fever and AST post-TACE (n = 34, r = 0.456, $p = 0.022$).

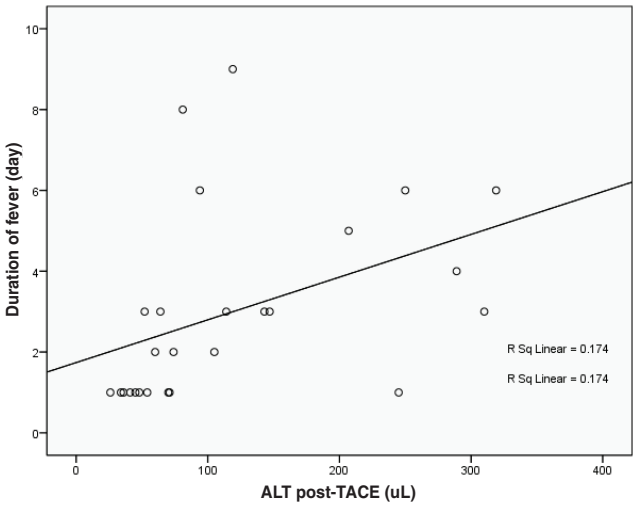

Figure 6. Correlations between duration of fever and ALT post-TACE (n = 34, r = 0.417, $p = 0.034$).

Table 4. Univariate analysis of potential predictors of post-TACE fever.

	Odds ratio	95% CI	*p*-value
Age (>55 years)	1.125	0.198-6.385	0.894
Albumin (<3.7 g/dL)	6.4	0.343-119.578	0.214
Total bilirubin (>1.2 mg/dL)	0.435	0.074-2.538	0.435
AST* (>80 U/L)	0	-	-
ALT* (>70 U/L)	0.107	0.016-0.726	0.220
LDH* (>500 U/L)	4.583	0.461-45.607	0.194
Platelet (<100,000/mL)	0.478	0.083-2.764	0.410
AFP (>200ng/mL)	3.10	-	0.999
Child-Pugh score (>5)	3.87	-	0.999
Tumor number (>1)	4.267	0.427-42.631	0.217
Tumor size (>5 cm)	5.70	-	0.998
Tumor volume (>100 cm^3)	7.456	-	0.998
Doxorubicin (>40 mg)	4.846	-	0.999
Mitomycin (>10 m)	3.127	-	0.999
Lipiodol (>8 mL)	0.092	0.092-9.507	0.954
Total dose delivered (>40)	6.05	-	0.998
Gelfoam embolization	16.0	1.873-136.696	0.011

*Before TACE

0.007), the dosage of chemoembolizing agents (r = 0.331, $p = 0.056$), elevation of post-procedure AST (r = 0.456 $p = 0.022$), and elevation of post-procedure ALT (r = 0.417, $p = 0.034$) respectively. The total dose delivery was significantly associated with as well as correlated with post-procedure elevation of serum AST and serum ALT (r = 0.568, $p = 0.001$, r = 0.520, $p = 0.003$, respectively) (figure not shown).

Potential predictive factors of post-TACE fever

From Table 4, it can be seen that only the use of gelform embolization appeared to be a significant predictive factor for post- TACE fever. Other parameters did not exhibit sufficiently good cut-points to be of predictive value for the occurrence of post TACE fever.

Discussion

TACE is a major treatment for unresectable HCC. Fever is a very common post-procedure side effect, triggering discomfort for patients, the relatives and physicians alike. Only a few studies have addressed the causes and the predictive factors of post-TACE fever, hence the varying practical management. In this study, we found that post-TACE fever was a common occurrence, with an incidence of 85% of 40 TACE sessions. The fever was usually self-limited without pre- or post-procedural antibiotic prophylaxis. No documented infection was observed. We also found that a larger tumor size, a higher chemoembolization dosage, and the use gelfoam embolization were the main factors predicting the occurrence of post-TACE fever.

Patients with longer duration of fever also had larger tumor(s) and were given higher dosages of chemoembolization agents. They were more likely to show higher transminase level post-procedure. The total dose delivery correlated with post-procedure AST and ALT elevations. Such findings would suggest that the cause of fever is likely from the process of tumor necrosis. Physicians, therefore, can prescribe just antipyretics such as NSAIDs for the fever. This would help reduce the cost of unnecessary septic workup, and should shorten the of hospital stay. It would also help reduce patient's discomfort and anxiety.

In our study, we found that HCC patients were predominantly male (97%), with a men age of 57, which was lower than in a previous study with a mean age of 65 yrs[18]. This difference may be due to early cirrhosis cascade from higher prevalence of chronic hepatitis infection in Thailand. Most of our cases had cirrhosis from hepatitis C infection (62.5%).

No difference was found with regard to the dura-

tion of fever between the effective and the ineffective cases in our study. This was in keeping with precious reports demonstrating that post-TACE fever did not correlate with an enhanced tumor response[18,25].

The pathogenesis of post-TACE fever is unclear. However, it may be assumed from previous studies[18] as well as from our study that the fever is on inflammatory response to hypoxic tumor necrosis. Castells et al. found that post-TACE fever represented extensive tumor necrosis[23]. Paye *et al*. suggested that post-TACE fever was related to tumor necrosis itself, or to collateral damage to non-tumorous liver tissue[19]. In our study, the levels of AST, ALT, LDH and CRP seemed higher in the fever group, and posibly reflected tumor necrosis. The use of gelfoam embolization that created permanent occlusion of the feeding to the vessels tumor was a significant predictor of fever post-procedure in our study. Fever could reflect the amount of tissue necrosis and inflammatory response to TACE. Infection rarely occurs, thanks to the standard aseptic procedural technique, although liver abscesses after TACE were reported at around 0.26%[26]. No infection was identified in our study population.

The occurrence of fever was common in our study, but no infective case was detected. We, therefore, recommend that antibiotic prophylaxis is not necessary either before TACE or after post TACE fever, and this is in agreement with previous studies[18,22,23]. In one study, post TACE fever responded well to NSAIDs[27]. The physician may prescribe an NSAID after completing the TACE procedure to avoid post TACE fever, or does so as soon as fever is detected. This may reduce patient's discomfort and shorten the length of hospital stay. Patients who had post TACE fever can be reassured and advised to be aware of an infection if fever does not subside after an NSAID course.

In Table 3, perform the statistical significant difference in hepatitis C status, pre-procedure ALT level between group that can not be explained, maybe accidental finding from too small population of control group (non-fever). We cannot identify the cut-off points of the biochemical tests prior to TACE to predict the occurrence of fever after the TACE procedure.

In our study, serum albumin fell significantly after TACE. Albumin is an acute phase reactant protein that reflects an inflammatory process. Elevation of serum AST level, and the other hand, reflects tissue necrosis. Falling albumin and rising AST may thus be used to predict the occurrence of post TACE -fever. Based on Pearson's correlation co-efficient analysis the size and the volume of tumor(s) as well as chemoembolization dosage appeared to correlate with the fever duration. Figure 3 and Figure 4, although there was no significant cut-point value to predict the occurrence of fever after TACE (Table 4). We demonstrated that the use of gelform embolization was the only predictive factor for post TACE fever, while larger tumor size, longer tumor volume, and chemoembolization dosage may be predictive of the likelihood of post-TACE fever.

In conclusion, post-TACE fever is a very common side effect in HCC patients undergoing TACE, but bacteremia and infectious complications are rare. Patients with larger tumor size, higher dosage of chemoembolization agent, and use of gelatin sponge for embolization are associated with a higher risk of post-procedure fever. Prophylaxis antibiotic may be unnecessary and antipyretics such as NSAIDs may be useful patients at high risk of developing post TACE fever. The cut-off point of biochemical tests as a predictor for post TACE fever were not identified. A larger control group in future study assesses meaningful cut-off points of biochemical tests. The pathogenesis of post-TACE fever is not well understood, but seemingly related to tumor necrosis as well as injury to adjacent normal healthy liver parenchyma.

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