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ORIGINAL ARTICLE

Effect of Transarterial Chemoembolisation in Unresectable Hepatocellular Carcinoma with Portal Vein Tumour Thrombosis: Single-centre Study

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ABSTRACT

Objectives: *To determine the effect of transarterial chemoembolisation (TACE) on liver function and procedure-related mortality in patients with unresectable hepatocellular carcinoma (HCC) and portal vein tumour thrombosis (PVTT).*

Methods: *This was a retrospective study of patients with HCC and PVTT who underwent TACE from January 2012 to December 2013 at a single tertiary medical centre in Hong Kong. Patient demographics, aetiology of cirrhosis, alpha fetoprotein (AFP) level, tumour size, number of tumours, liver function (total bilirubin, albumin, international normalised ratio [INR]), and Child-Pugh score were evaluated before and 4 weeks after TACE. The 30-day mortality was also recorded.*

Results: *TACE was performed in 26 patients with unresectable HCC and PVTT (mean age, 61 years). The mean total bilirubin level before and after TACE was 18.2 μmol/l and 26.8 μmol/l (p = 0.140), respectively, and mean albumin level fell from 36.8 g/l to 33.9 g/l (p = 0.009). The respective mean INR before and after TACE was 1.1 and 1.2 (p = 0.120), the AFP level was 35,364.0 ng/ml and 37,424.5 ng/ml (p = 0.563), and the mean Child-Pugh score was 6.0 and 6.6. The mean and median survival of patients was 5.1 months (range, 1.5-8.8 months) and there was no 30-day mortality.*

Conclusion: *TACE has a deteriorating effect on liver function in patients with unresectable HCC and PVTT. Nonetheless since there were no procedure-related deaths and TACE has potential survival benefits, it should be a treatment option along with superselective catheterisation of tumour feeding vessels for patients with HCC and PVTT.*

Key Words: *Carcinoma, hepatocellular; Chemoembolization, therapeutic; Liver neoplasms; Portal vein; Thrombosis*

中文摘要

經肝動脈栓塞化療對不能切除肝癌患者合併門靜脈癌栓的影響：單中心研究

蕭廣樂、朱炳容、劉漢威、陳積聖、葉筱筠

目的：探討經肝動脈栓塞化療（TACE）對於合併門靜脈癌栓（PVTT）的肝癌患者在肝功能和手術相關死亡率的影響。

方法：本回顧研究在香港一所三級醫療服務的醫院內完成，對象是在2012年1月至2013年12月期間有

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PVTT的肝癌患者。在進行TACE前和4週後記錄病人肝硬化的病因、α-胎蛋白（AFP）水平、腫瘤大小、腫瘤數目、肝功能指數（總膽紅素、白蛋白、國際標準化比率〔INR〕）和Child-Pugh評分。記錄患者30天死亡率。

結果：共26例有PVTT並不能切除的肝癌患者進行TACE，平均年齡61歲。進行TACE前後的平均總膽紅素水平分別為18.2 μmol/l和26.8 μmol/l（p=0.140），白蛋白平均水平從36.8 g/l下降至33.9 g/l（p=0.009），而相應的INR平均值為1.1和1.2（p=0.120）、AFP水平為35,364.0 ng/ml和37,424.5 ng/ml（p=0.563）、Child-Pugh平均分數為6.0和6.6。患者的平均和中位生存期為5.1個月（介乎1.5-8.8個月）。無30天內死亡率患者。

結論：TACE能令有PVTT肝癌患者肝功能下降。由於沒有手術相關的死亡病例，而TACE有利於患者的生存期，對於有PVTT的肝癌患者來說，TACE合併富血供腫瘤施以超選擇插管治療可作為一種選擇。

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the third most frequent cause of cancer-related death worldwide.[1,2] Treatment methods include liver resection, liver transplantation, local ablation, chemoembolisation, and systemic therapies. A large number of patients with HCC, however, are diagnosed at an intermediate or even advanced stage when curative therapy is no longer possible.[3] According to a systematic review, chemoembolisation improves the survival of patients with unresectable HCC and should be the standard treatment option.[4]

HCC complicated by portal vein tumour thrombosis (PVTT) is an extremely poor prognostic indicator with a mean survival time of 2 to 4 months.[5-7] PVTT causes stenosis or even portal vein occlusion, decreases the blood supply to the normal liver parenchyma, and causes acute liver failure. It then limits the application of transarterial chemoembolisation (TACE) in HCC. Thus PVTT is traditionally considered a contraindication to TACE.[8,9]

Despite this, several studies have shown that TACE can be safely performed in HCC patients with PVTT and survival can be improved.[10-12] A recent meta-analysis concluded that TACE is a safe treatment for advanced HCC with PVTT. It has a potential survival benefit even in the presence of main portal vein obstruction.[13] In view of the large amount of supporting evidence, we conducted a retrospective study of HCC patients with PVTT to review the effect of TACE on liver function and procedure-related mortality so as to determine the safety and efficacy of TACE.

METHODS

Patients

This retrospective study was approved by the clinical and research ethics committee of the Hong Kong New Territories West Cluster; the requirement to obtain informed consent was waived. We reviewed the electronic medical records of patients with HCC and PVTT who had undergone TACE from January 2012 to December 2013 in Tuen Mun Hospital, a local tertiary referral centre in Hong Kong.

The diagnosis of HCC was based on the guidelines of the European Association for the Study of the Liver (EASL) or American Association for the Study of Liver Diseases (AASLD).[3,14] The presence of PVTT was confirmed by the demonstration of a low-attenuation intraluminal mass expanding the portal vein and / or filling defects in the main portal vein (MPV) on three-phase dynamic computed tomography (CT).[15] Survival time was counted from the first day of diagnosis by CT scan until the patient died.

Patient demographics, aetiology of cirrhosis, tumour factors including alpha fetoprotein (AFP) level, and tumour size and number were recorded. Baseline liver function (total bilirubin, albumin, international normalised ratio [INR]), Child-Pugh score,[4,16] and clinical symptoms including ascites and hepatic encephalopathy were evaluated prior to TACE. These parameters were reassessed 4 weeks following TACE. Technical factors including dose of cisplatin / lipiodol mixture used and gelatin particle embolisation were recorded. We also recorded the 30-day mortality, defined as procedure-related death.

Procedures

TACE was performed as superselective as possible through the lobar, segmental, or subsegmental arteries using a microcatheter (Renegade HI-FLO Microcatheter; Boston Scientific, Cork, Ireland). A mixture (1:1 ratio) that comprised cisplatin (Pharmachemie B. V., Haarlem, The Netherland) and lipiodol (Andre Guerbet; Aulnay-sous-Bois, France) was administered into the feeder vessels. Thereafter, gelatin sponge particle (Upjohn, Kalamazoo [MI], USA) mixed with contrast material was administered into the feeder vessels until stasis of arterial flow was achieved. Gelatin administration was avoided in patients in whom flow of feeder vessels already had achieved stasis following cisplatin injection.

Statistical Analyses

Continuous variables were summarised as the mean values, and categorical variables were expressed as frequencies. Overall survival was measured from the date of TACE procedure to death from any cause. Variables included in the analysis were gender (female vs. male), age, ascites (present or absent), hepatic encephalopathy (present or absent), cause of cirrhosis (hepatitis B or non–hepatitis B), AFP level, albumin level, total bilirubin level, Child-Pugh score, and number of tumour lesions (1 or ≥2). A p value of <0.05 was considered indicative of a statistically significant difference. All statistical calculations were performed using the Statistical Package for the Social Sciences (Windows version 18.0; SPSS Inc, Chicago [IL], USA), and paired T test was applied.

Table 1. Baseline characteristics of patients.

Characteristic	No. (%) of patients or mean value
Gender	
Male	20 (77%)
Female	6 (23%)
Age (years)	61
Causes of cirrhosis	
Hepatitis B	19 (73%)
Non–hepatitis B	7 (27%)
No. of tumours	
1	14 (54%)
≥2	12 (46%)
Tumour size (cm)	
<10	15 (58%)
≥10	11 (42%)
Embolisation	
Gelform given	8 (31%)
Gelform not given	18 (69%)
Cisplatin / lipiodol mixture (ml)	19

RESULTS

During the enrolment period, a total of 435 TACE procedures were performed of which 26 were in patients with unresectable HCC with PVTT. The baseline characteristics are summarised in Table 1. Hepatitis B virus infection was a common aetiology (73%). Before TACE, 16 patients were Child-Pugh class A and 10 patients were Child-Pugh class B. None were Child-Pugh class C. Most patients had unilobar portal vein thrombosis although one had main portal vein thrombosis. The mean Child-Pugh score is shown in Table 2. Four weeks following TACE, one patient became Child-Pugh class C, 12 patients class B, and 13 patients class A. The number of tumour lesions was 1 and ≥2 in 14 and 12 patients, respectively. The size of tumour was <10 cm and ≥10 cm in 15 and 11 patients, respectively. The mean cisplatin / lipiodol mixture injected was 19 ml.

After TACE, the AFP, total bilirubin, and INR levels increased, although no statistical significance was attained. The albumin level reduced from 36.8 g/l to 33.9 g/l (p = 0.009). Ascites was evident in eight patients before and in 11 patients 4 weeks after TACE (p = 0.110). No hepatic encephalopathy was detected before or after TACE. The Child-Pugh score was 6.0 before and 6.6 after TACE (p = 0.029) [Table 2]. No

Table 2. Laboratory tests (range) and Child-Pugh score.

	Mean (range) or No.		p Value
	Before TACE	4 weeks after TACE	
AFP level (ng/ml)	35,364.0 (1-484,000)	37,424.5 (1-489,014)	0.563
Total bilirubin (μmol/l)	18.2 (5-49)	26.8 (5-192)	0.140
Albumin (g/l)	36.8 (30-47)	33.9 (25-46)	0.009
INR	1.1 (1.0-1.3)	1.2 (1.0-1.8)	0.120
No. of ascites	8	11	0.110
Hepatic encephalopathy	0	0	0
Child-Pugh score	6.0 (5-8)	6.6 (5-11)	0.029

Abbreviations: AFP = alpha fetoprotein; INR = international normalised ratio; TACE = transarterial chemoembolisation.

patient died within 30 days of the procedure.

Statistical analysis revealed that treatment with TACE in patients with HCC and PVTT resulted in a statistically significant drop in albumin level 4 weeks later. Although the remaining blood parameters revealed no significant changes, they did show mild deterioration as reflected by the Child-Pugh score that increased from 6.0 to 6.6. Nonetheless there were no procedure-related deaths and the mean survival of patients was 5.1 months (range, 1.5-8.8 months). The median survival was also 5.1 months. Our results demonstrate that TACE can be performed relatively safely in patients with HCC and PVTT.

DISCUSSION

In the current AASLD guidelines, the presence of PVTT remains the main contraindication for TACE.[14] This is based on the therapeutic risk of acute liver failure.[8,9] Therapeutic options for these patients with unresectable HCC and PVTT are limited. Only systemic chemotherapy or administration of molecular-targeted agents such as sorafenib is recommended.[17,18] In a study by Uka et al,[19] more than 90% of patients with unresectable HCC and PVTT died of intrahepatic tumour. It is therefore reasonable to provide different treatment options for this group of patients.

In Asia, many clinicians still consider TACE to be a useful treatment for patients with unresectable HCC and PVTT,[20] and several studies attest to its safety. The survival benefit of TACE in comparison with conservative treatment provides supportive evidence.[21-23] The results of survival in these studies ranged from 5 to 8.7 months, compared with 2 to 4 months following conservative treatment.[5-7] Thus TACE should remain a treatment option in this patient population.

The overall complication rate following TACE is about 10% in the presence of a patent portal vein.[24] Complications include postembolisation syndrome, hepatic failure, pulmonary embolism, acute renal failure, infection, biliary infarction, and gastrointestinal bleeding. In the setting of PVTT, more TACE-related toxicity and fatal complications are expected. Indeed, HCC with PVTT has been reported to be an important predisposing factor for acute liver failure following TACE.[25,26] For this reason, the procedure has long been contraindicated. Theoretically, a superselective chemoembolisation technique can be adopted so as to minimise normal liver parenchymal damage. In addition, the occurrence of fatal complications can be minimised, especially in patients with well-developed collateral circulation around the portal trunk. Further, no procedure-related deaths were reported after TACE.[27] The results of our study demonstrated similar findings with no 30-day mortality and further support the use of TACE as a treatment option.

Contrary to this view, the Barcelona Clinic Liver Cancer group and AASLD guidelines recommend sorafenib as the sole standard treatment for advanced HCC.[3,14] A study by Pinter et al[28] showed that the median overall survival was 7.4 months (confidence interval, 5.6-9.2 months) for patients treated with sorafenib alone. There was no significant difference when compared with the group treated with conventional TACE plus lipiodol or drug-eluting bead in whom survival was 9.2 months (range, 6.1-12.3 months; $p = 0.377$).[28] Although Pinter et al's study[28] was retrospective in nature, the findings challenge the current recommendation and support the use of TACE in selected patients with advanced HCC.

The mean and median survival in our study was 5.1 months, which is slightly higher than the reported mean survival following conservative treatment (2-4 months).[5-7] More importantly, no procedure-related deaths were recorded, consistent with results from the use of sorafenib. The prohibitive cost of sorafenib, however, likely precludes its use in the majority of HCC patients who would nonetheless benefit.

Recent reports support Yttrium internal irradiation as the standard care for PVTT HCC. Experience at our institution is limited but a recent review[29] stated that transarterial radioembolisation (TARE) on average produces disease-control rates exceeding 80% and is a consolidated therapy for HCC.

Current data are all based on retrospective series or non-controlled prospective studies since randomised controlled trials comparing TARE with other liver-directed therapies for intermediate and locally advanced stage HCC are still in progress. The AASLD, EASL, and the European Organization for Research and Treatment of Cancer do not include TARE in their guidelines.[14]

There are a few limitations of our study. It was retrospective in nature, and measurement of subjective symptoms such as pain was not included. The number of cases was not sufficiently large to be representative

and there was no control group. Also, there were no Child-Pugh class C patients although this was likely to be too advanced disease for any treatment. Finally, data beyond 4 weeks after TACE were not available.

CONCLUSION

TACE has a deteriorating effect on liver function in patients with HCC and PVTT. Nonetheless the absence of any procedure-related deaths and the potential survival benefits support the use of TACE with superselective catheterisation of tumour feeding vessels as a treatment option for patients with HCC and PVTT.

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