Cancer Biol Med 2016. doi: 10.20892/j.issn.2095-3941.2016.0059

REVIEW

Portal vein tumor thrombus is a bottleneck in the treatment of hepatocellular carcinoma

Ju-Xian Sun[1*], Jie Shi[1*], Nan Li[1], Wei-Xing Guo[1], Meng-Chao Wu[1], Wan-Yee Lau[2], Shu-Qun Cheng[1]

[1]Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgical Hospital, Shanghai 200438, China; [2]Faculty of Medicine, Chinese University of Hong Kong, Hong Kong, SAR 999077, China

ABSTRACT The effect of portal vein tumor thrombus (PVTT) on the prognosis of patients with hepatocellular carcinoma has become clear over the past several decades. However, identifying the mechanisms and performing the diagnosis and treatment of PVTT remain challenging. Therefore, this study aimed to summarize the progress in these areas. A computerized literature search in Medline and EMBASE was performed with the following combinations of search terms: "hepatocellular carcinoma" AND "portal vein tumor thrombus." Although several signal transduction or molecular pathways related to PVTT have been identified, the exact mechanisms of PVTT are still largely unknown. Many biomarkers have been reported to detect microvascular invasion, but none have proved to be clinically useful because of their low accuracy rates. Sorafenib is the only recommended therapeutic strategy in Western countries. However, more treatment options are recommended in Eastern countries, including surgery, radiotherapy (RT), transhepatic arterial chemoembolization (TACE), transarterial radioembolization (TARE), and sorafenib. Therefore, we established a staging system based on the extent of portal vein invasion. Our staging system effectively predicts the long-term survival of PVTT patients. Currently, several clinical trials had shown that surgery is effective and safe in some PVTT patients. RT, TARE, and TACE can also be performed safely in patients with good liver function. However, only a few comparative clinical trials had compared the effectiveness of these treatments. Therefore, more randomized controlled trials examining the extent of PVTT should be conducted in the future.

KEYWORDS Biomarkers; surgery; transhepatic arterial chemoembolization; sorafenib; review

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and third most common cause of cancer-related deaths worldwide[1]. Despite advances in the diagnostic and treatment strategies for different HCC stages, the survival of patients with HCC is still poor. For the past 20 years, the 5-year recurrence rate remains at approximately 70% after R0 resection[2] and 5%–30% after liver transplantation[3]. Sorafenib is the only drug that extends the overall survival time of patients with advanced HCC by approximately three months[4]. Effectively addressing portal vein invasion in the form of macro-portal vein tumor thrombus (PVTT) or micro-PVTT may improve treatment results for HCC.

The effect of PVTT on the prognosis of patients after treatment has become clear over the past several decades. Without treatment, the median survival time for patients with macro-PVTT is 2.5–4 months compared with 10–24 months for patients without macro-PVTT. Macro-PVTT is the single most important independent risk factor of early postoperative recurrence in HCC[5]. Macro-PVTT is also an absolute contraindication of liver transplantation (LT). The presence of macro-PVTT indicates that the disease is in Barcelona Clinic Liver Cancer (BCLC) C stage. Even microscopic PVTT exhibits a significant, negative prognostic effect on patients who underwent LT and liver resection. For patients who underwent LT, the 3-year cumulative recurrence rate exceeds the Milan criteria; however, the recurrence rates for patients without microscopic PVTT is within the Milan criteria and is lower than that of patients with microscopic PVTT[6]. For patients who underwent liver resection, microscopic PVTT significantly decreases 3-year (RR = 1.82) and 5-year (RR = 1.51) disease-free survival[7]. No accurate, objective, or reproducible method is available for evaluating the presence of microscopic PVTT prior to surgery. Therefore, it is necessary to add information

* These authors contributed equally to this article.
Correspondence to: Shu-Qun Cheng
E-mail: chengshuqun@aliyun.com
Received July 13, 2016; accepted August 17, 2016.
Available at www.cancerbiomed.org

obtained from surgery on microscopic PVTT to the currently available HCC staging systems and LT criteria. In this article, we will review PVTT from the perspectives of incidence and molecular mechanisms, as well as the current knowledge on the diagnosis and treatment of PVTT.

A computerized literature search in Medline and EMBASE was performed with the following combinations of search terms: "hepatocellular carcinoma" AND "portal vein tumor thrombus." Only English- and Chinese-language articles were searched. The last search update was performed in June 2015. We also manually searched articles for additional citations.

Incidence of PVTT

We found that PVTT incidence was considerably higher than previously expected. HCC is prone to invading the portal venous system. Approximately 10%–40% of patients exhibit macroscopic PVTT when HCC is first diagnosed[8]. The incidence of macroscopic PVTT is 5.4%–26.0% in patients who underwent hepatectomy[9,10], 11.3%–38.0% in patients who received non-surgical therapy[11,12], and 44.0%–62.2% at autopsy[13]. The incidence of micro-PVTT is even higher and is present in 20% of tumors with diameters of 2 cm, 30%–60% in tumors with diameters of 2–5 cm, and 60%–90% in tumors with diameters of > 5 cm[14]. Data from 5,524 patients with HCC and who underwent liver resection at our hospital (Eastern Hepatobiliary Surgical Hospital, Shanghai, China) from 1960 to 1998 showed that the incidences of macro-and micro-PVTT were 6.1% and 67.1%, respectively[15].

Mechanisms of PVTT formation

Until recently, the mechanisms of PVTT formation have largely remained unknown. As the majority of PVTT emerges around the primary tumor (aPVTT), the traditional belief is that PVTT develops following the direct invasion of a liver tumor, resulting in a hepatic artery-portal vein fistula and portal vein countercurrent. However, we detected distinct PVTT (dPVTT), a unique type of PVTT distant from the liver tumor nodule[16]. Comparative proteomics showed that dPVTT possessed molecular signatures different from those of liver tumors, implying that the mechanism of PVTT formation is far more complicated than previously thought.

The lack of an experimental model hinders research progress on PVTT, and the primary culture of PVTT cells was previously considered as virtually impossible. However, after four years of unremitting efforts, we successfully established two PVTT-originating HCC cell lines, CSQT-1 and CSQT-2, by culturing PVTT cells from more than 60 PVTT patients. This cell model provides a solid foundation for future basic research[17].

We conducted numerous successful experimental assessments on CSQT-1 and CSQT-2, such as advanced microRNA (miRNA) and cDNA microarray analyses. In addition, we established a corresponding animal model. We found that miRNA-135a is highly overexpressed in CSQT-2 and is related to the prognosis and survival of patients with both HCC and PVTT. Experiments conducted with a nude mouse model showed that blocking miR-135a expression significantly reduces PVTT incidence. We then identified the upstream forkhead box M1 (FOXM1) and downstream metastasis suppressor 1 (MTSS1) of miR-135a. Finally, we established the FOXM1-miR-135a-MTSS1 pathway[18].

Chronic hepatitis B virus (HBV) is an important etiological cause of HCC. However, the relationship between HBV and PVTT is still unclear. Therefore, we participated in a study conducted by researchers at Duke University that examined the role of HBV infection in microenvironmental changes[19]. We found that PVTT development is positively related to HBV infection status and transforming growth factor (TGF)-β activity. We then found that miRNA-34a, a tumor suppressor, is negatively associated with TGF-β activity. We developed and performed a qPCR-based assay to demonstrate that CCL22, a chemokine gene, is the primary target of miRNA-34a. In addition, we found that an inverse relationship exists between miRNA-34a and CCL22 levels. Finally, we validated the relationship between Treg cells and chemokine CCL22. Our results established the HBV-TGF-β-miRNA-34a-CCL22-Treg-PVTT pathway. In our opinion, this is the most complete molecular pathway explaining PVTT development.

Other micro-RNAs and genes also significantly contribute to PVTT development. Abnormalities in coagulation and fibrinolysis systems and angiogenesis, as well as in many adhesion molecules and chemokines, are associated with PVTT formation. Unfortunately, all of these factors still cannot be applied clinically as PVTT biomarkers.

Biomarkers for PVTT

Current imaging techniques cannot detect microvascular invasion in the third or more proximal ramifications of the main portal vein. Attempts to identify one or more serum markers to accurately predict PVTT had been unsuccessful.

In a retrospective study involving 1,452 patients with HCC with or without PVTT, the cut-off value of >20, 000 ng/mL

for α-fetoprotein has a specificity of 96% and a sensitivity of only 76%[20]. MiRNAs have been used as biomarkers for HCC, but not for PVTT. A group of 20-miRNA tumor signatures were acquired by comparing the miRNA profiles of 241 patients with HCC. The corresponding non-tumorous liver tissues significantly predicted HCC with venous metastases, but not PVTT[21]. A five-protein signature including 3478, 2022, 8901, 9415, 8773, 2766, and 2745 showed a sensitivity of only 75.8% and specificity of 82.3% for predicting PVTT[22]. Other potential biomarkers include des-gamma-carboxy prothrombin (DCP), thrombus precursor protein, and alfa-l-fucosidase. However, further studies are required to confirm their usefulness as PVTT biomarkers.

As no clinically useful, specific biomarkers are available, combinations of other detection methods have also been studied. Several studies exhibit potential clinical value. One study[23] combined a cut-off value of 101 mAU/mL for serum DCP with a cut-off value of 3.6 cm for tumor diameter and a SUVmax of 4.2. The sensitivity for PVTT diagnosis was 100% and specificity was 90.9% if patients with HCC showed two of these three features. However, these results necessitate further validation in large-scale studies.

Therapeutic interventions for PVTT

Eastern and Western countries have widely different treatment approaches for HCC and PVTT[1,24]. Sorafenib is the only recommended therapeutic strategy by EASL guidelines. However, Asia-Pacific guidelines recommend several treatment options, including surgery, radiotherapy (RT), transhepatic arterial chemoembolization (TACE), and sorafenib. The high incidence of PVTT in Eastern countries is an important reason for these different treatment approaches. As other therapeutic methods, such as RT and TACE, are also used to treat PVTT patients, it is necessary to establish a staging system with prognostic value to determine the long-term survival of HCC patients with PVTT. Referring to the results of a cohort study we published in 2007[25], PVTT can be classified into four grades according to the extent of PVTT in the portal vein: type I, wherein a tumor thrombus is present in the segmental branches of the portal vein or above; type II, wherein the tumor thrombus is present in the right or left portal vein; type III, wherein the tumor thrombus is present in the main portal vein trunk; and type IV, wherein the tumor thrombus extends from the portal vein to the superior mesenteric vein. This classification system effectively predicts the long-term survival of patients after surgery[26] or TACE[27]. Therefore, this classification is useful for clinical decision-making processes in HCC treatment.

Surgery

Advances in surgical techniques have enabled the safe resection of both hepatic tumors and PVTT. Currently, patients with PVTT who exhibited varying degrees of portal vein involvement have a perioperative mortality of 0%–5.9%, with median survival time ranging from 8.9 months to 33 months[8]. Patients with type I/II PVTT have a reported perioperative mortality of 0% to 3.1%[26,28,29], with a 5-year overall survival rate of 10%–59%[9,28,30,31], which is considerably higher compared with patients with type III/IV PVTT (perioperative mortality, 0%–28%; 5-year overall survival rate, 0%–26.4%)[10,29,31,32] (**Table 1**). Furthermore, the obstruction of the portal vein in patients with type III/IV PVTT can result in deteriorated liver function, cause refractory ascites, and induce variceal bleeding from the lower esophagus. A thrombus should be surgically removed if a patient's liver function permits concomitant hepatic resection. However, additional clinical trials are necessary to examine this treatment approach. Prognosis is unaffected by different surgical methods, including en bloc resection of a liver tumor and PVTT, thrombectomy, or even peeling off a PVTT[9]. Surgical resection margin (SM) should be attempted in patients with infiltrative PVTT growth. In a retrospective study that included 381 patients, Zhou et al.[33] reported that a SM of > 5 mm is an independent prognostic factor for ICC. Meta-analysis[34] showed that patients with type I/II PVTT and who underwent surgery have better survival rates than those who underwent TACE. However, TACE is suitable for patients with type III/IV.

A randomized controlled trial (RCT) studying the effectiveness of postoperative TACE[35] demonstrated that TACE delays postoperative recurrence. Preoperative irradiation is beneficial for patients with PVTT, as it can shrink PVTT, induce hypertrophy of the contralateral liver, and decrease tumor recurrence rate[36]. We are now evaluating the efficacy of sorafenib in delaying postoperative recurrence in patients with PVTT, and the initial results are encouraging (data not shown).

TACE

Given the potential risk of liver failure and the limited benefits associated with TACE, some researchers had

Table 1 Hepatectomy and TACE for PVTT patients

First author	Year	Treatment	*n*	Cheng's type (*n*)	5-year survival rate, %	Median survival time, months
Wu CC [29]	2000	Surgery	112	I-II (97)	28.5	-
				III (15)	26.4	-
Poon RT [32]	2003	Surgery	20	II-III	13.3	6.0
Ikai I [31]	2006	Surgery	78	II (35)	10.1	11.4
				III (43)	12.0	8.9
Chen XP [28]	2006	Surgery	438	I-II (286)	18.1	18.8
				III (152)	0	10.1
Shi J [26]	2010	Surgery	406	I (139)	25.1 (3-year)	22
				II (169)	17.7 (3-year)	15
				III (78)	3.6 (3-year)	10
				IV (20)	0 (3-year)	8
				II-IV (1021)	18.3	-
Peng ZW [50]	2012	Surgery	201	I (27)	37.9 (3-year)	-
				II (68)	17.2 (3-year)	-
				III (83)	3.6 (3-year)	-
				IV (23)	0 (3-year)	-
Liu PH [30]	2014	Surgery	247	I-II	59	64
Kim KM [39]	2009	TACE	149	I-II (57)		
				CP Class A	-	10.2
				CP Class B	-	5.5
				III (92)		
				CP Class A	-	5.3
				CP Class B	-	4.7
Luo J [40]	2011	TACE	84	I/II (40)	-	10.2
				III (44)	-	5.3
Niu ZJ [27]	2012	TACE	115	I (12)	-	12
				II (52)	-	8.3
				III (42)	-	5
				IV (9)	-	2.43
Peng ZW [50]	2012	TACE	402	I (54)	8.9 (3-year)	-
				II (136)	6 (3-year)	-
				III (166)	4.2 (3-year)	-
				IV(46)	4.3 (3-year)	-
Liu L [42]	2014	TACE	188	I-II (98)		
				CP Class A	-	9.8
				CP Class B	-	5.6
				III (90)		
				CP Class A	-	4.3
				CP Class B	-	3.4
Liu PH [30]	2014	TACE	181	I-II (181)	50 (3-year)	32

previously suggested that it should not be administered to patients with PVTT, especially to those with type III/IV PVTT. Nevertheless, evidence indicates that TACE can be performed safely and feasibly in select patients with good liver function and adequate collateral circulation around the occluded portal vein regardless of PVTT extent[27]. Since 2010, the 30-day mortality has been reported[37] to be < 1.2%. The reported median survival time for patients with all PVTT types who received TACE is between 5.6 and 8.7 months[27,37-40]. Niu[27] reported that the overall median survival time for patients with types I, II, III, and IV PVTT and who received TACE were 19.0, 11.0, 7.0, and 4.0 months, respectively, which was significantly longer than that of patient groups with corresponding PVTT types and who did not receive TACE ($P < 0.01$). Liver function status also greatly influences survival; patients with Child A live longer (median: 7.4–11 months) than those with Child B (median: 2.8–4 months)[37,39,41,42]. However, no complete remission (CR) has been reported after TACE. Partial response is achieved in 19.5%–26.3% with a stable disease rate of 42.5%–62.7%[40,42,43]. A significant difference is observed in median survival between TACE responders (10.5 months) and non-responders (5.5 months)[38]. The use of small embolic particles and superselective chemoembolization reduces fatal complications and achieves increased response rates[37,38] (**Table 1**).

RT

In the past, radiation was rarely used alone and was usually combined with TACE or other treatments given the liver's low tolerance to external RT. The rapid progress in RT techniques has enabled the delivery of high radiation doses to HCC and PVTT without significantly increasing radiation toxicity. Published articles had reported significantly different total RT doses because of the differences in RT techniques and entry criteria. Reported RT doses vary from 17.5 Gy to 60 Gy in the 1.8–4.5 Gy fraction with response rates of 27.9%–53.8% and a CR of 0%–16.7%; the median survival time for responders and non-responders was 10.7–22 and 5–7.2 months, respectively[44,45]. Severe RT-related toxicity is rarely reported in patients with PVTT, but HBV reactivation should be monitored[45]. Hypofractionation enhances the effects of RT, but requires highly precise, image-guided radiation therapy techniques. The benefits of proton beam therapy are also increasingly apparent. The reported median survival duration can reach 13.2–22 months when combined with other treatments[46]. However, these results require large-scale verification. The RT plan should be formulated individually in the future according to tumor and PVTT location, liver function status, and other ongoing treatments.

Transarterial radioembolization (TARE)

TARE is a special type of TACE utilizing iodine-131-labeled lipiodol (^{131}I) or yttrium-90 (^{90}Y) as a cytotoxic agent in the hepatic artery. The effect of ^{131}I in patients with PVTT is controversial and still under investigation. ^{90}Y, a β-emitting isotope, is the most popular radioembolization agent. TARE exhibits comparable efficacy with TACE for advanced HCC[47]. TARE has a low risk of liver ischemia because of the minimal embolic effects of the ^{90}Y-glass microsphere. Therefore, TARE is suitable for patients with PVTT[48]. The response rate is 28%–50%, and the median survival time is 3.2–10.4 months for patients with all PVTT types[8].

Sorafenib

Sorafenib is an oral multi-tyrosine kinase inhibitor, and is the only drug that improves survival in patients with advanced HCC. However, a SHARP trial demonstrated that tumor response to sorafenib treatment is only 2%–3%[4]. A subgroup analysis of patients with PVTT showed that the median survival time of the sorafenib group was 8.1 months compared with the 4.9 months of the placebo group[49]. The incidence of severe adverse events can be as high as 9.4%–14.6% with sorafenib, and some patients may require reduced doses or even treatment interruption[4]. Only a few clinical trials had compared sorafenib with other treatment methods. Nakazawa[44] reported that RT significantly improves survival in patients with PVTT compared with sorafenib (10.9 *vs.* 4.8 months, respectively; $P = 0.025$).

Conclusions

PVTT incidence is much higher than expected. Currently, the mechanisms of PVTT occurrence remain largely unknown. Although many biomarkers have been reported, none have been shown to be clinically useful because of their low accuracy rates. Combining other investigatory methods, such as clinical imaging, can provide a possible solution to the lack of useful PVTT biomarkers. Great differences exist in PVTT treatment paradigms between Western and Eastern countries. Surgery is effective and safe in select patients with PVTT. RT is an alternative treatment. More RCTs should be conducted to examine the extent of PVTT.

Acknowledgements

This work was supported by grants from the Science Fund for

Creative Research Groups (Grant No. 81221061), The State Key Project on Diseases of China (Grant No. 2012zx10002016016003), The China National Funds for Distinguished Young Scientists (Grant No. 81125018), Chang Jiang Scholars Program (2013) of Chinese Ministry of Education, The National Key Basic Research Program (Grant No. 2015CB554000), National Natural Science Foundation of China (Grant No. 81101831, 81101511, and 81472282), The New Excellent Talents Program of Shanghai Municipal Health Bureau (Grant No. XBR2011025), Shanghai Science and Technology Committee (Grant No. 134119a0200), Shanghai Science and Technology Development Funds (Grant No. 14QA1405000), SMMU Innovation Alliance for Liver Cancer Diagnosis and Treatment (Grant 2012), General Program from Shanghai Municipal Health Bureau (Grant No. 20124301), and Shanghai Rising-star Program from Shanghai Science and Technology Committee (Grant No.13QA 1404900).

Conflict of interest statement

No potential conflicts of interest are disclosed.

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Cite this article as: Sun J, Shi J, Li N, Guo W, Wu M, Lau W, et al. Portal vein tumor thrombus is a bottleneck in the treatment of hepatocellular carcinoma. Cancer Biol Med. 2016; 13: 452-8. doi: 10.20892/j.issn.2095-3941.2016.0059