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REVIEW

Effective treatment strategies other than sorafenib for the patients with advanced hepatocellular carcinoma invading portal vein

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Abstract

Patients with hepatocellular carcinoma (HCC) accompanying portal vein tumor thrombosis (PVTT) have relatively few therapeutic options and an extremely poor prognosis. These patients are classified into barcelona clinic liver cancer stage C and sorafenib is suggested as the standard therapy of care. However, overall survival (OS) gain from sorafenib is unsatisfactory and better treatment modalities are urgently required. Therefore, we critically appraised recent data for the various treatment strategies for patients with HCC accompanying PVTT. In suitable patients, even surgical resection can be considered a potentially curative strategy. Transarterial chemoembolization (TACE) can be performed effectively and safely in a carefully chosen population of patients with reserved liver function and sufficient collateral blood flow nearby the blocked portal vein. A recent meta-analysis demonstrated that TACE achieved a substantial improvement of OS in HCC patients accompanying PVTT compared with best supportive care. In addition, transarterial radioembolization (TARE) using yttrium-90 microspheres achieves quality-of-life advantages and is as effective as TACE. A large proportion of HCC patients accompanying PVTT are considered to be proper for TARE. Moreover, TACE or TARE achieved comparable outcomes to sorafenib in recent studies and it was also reported that the combination of radiotherapy with TACE achieved a survival gain compared to sorafenib in HCC patients accompanying PVTT. Surgical resection-based multimodal treatments, transarterial approaches including TACE and TARE, and TACE-based appropriate combination strategies may improve OS of HCC patients accompanying PVTT.

Key words: Sorafenib; Hepatocellular carcinoma; Portal vein; Thrombosis

Core tip: Given the modest survival gain and the limitation of sorafenib, such as resistance and tolerability, there are still clinical unmet needs in the management of patients with hepatocellular carcinoma (HCC) accompanying portal vein tumor thrombosis (PVTT). Surgical

resection-based multimodal treatments including liver transplantation and transarterial chemoembolization-based appropriate combination strategies for resectable HCC accompanying PVTT may improve overall survival in these patients.

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INTRODUCTION

Globally, hepatocellular carcinoma (HCC) is one of the main reasons of malignancy related death[1,2]. Most HCCs are detected in an advanced stage in spite of surveillance programs for high risk populations, and the prognosis for these patients is poor. Consequently, a minority of patients is eligible for liver resection.

Portal vein tumor thrombosis (PVTT) arises in about 10%-40% of patients at diagnosis[3-5]; lower rates are reported when HCC is diagnosed early usually as a consequence of screening[3] and is apparent in up to 44% of patients with HCC at the end of life[6]. PVTT has a profound adverse effect on prognosis, with the median survival time of patients with unresectable HCC accompanying PVTT being significantly reduced (2-4 mo) compared to those not accompanying PVTT (10-24 mo)[4,5,7]. The range and position of PVTT further affect the prognosis. PVTT is related with poor prognosis probably because of the intensified risk of tumor spread, raised portal pressure inducing variceal bleeding and reduced portal flow causing jaundice, ascites, hepatic encephalopathy and hepatic failure[4,8].

The Liver Cancer Study Group of Japan suggested a macroscopic classification for PVTT: categorized into five grades, Vp0-Vp4 (Figure 1). Each one is defined as follows: no PVTT, Vp0; existence of PVTT not in, but distal to, the 2nd-order branches of the portal vein, Vp1; existence of PVTT in the 2nd-order branches of the portal vein, Vp2; existence of PVTT in the 1st-order branches of the portal vein, Vp3; and existence of PVTT in the main trunk of the portal vein or a portal vein branch contralateral to the mainly involved lobe (or both), Vp4[9]. This classification is helpful, because it is established by surgical outcomes and by the clinical, imaging, and pathological findings.

The presence of PVTT also limits the treatment options, with HCC treatment guidelines often considering PVTT a contraindication for transplantation, curative resection and transarterial chemoembolization (TACE)[10-12]. Current guidelines recommend sorafenib for the patients with HCC with PVTT. Sorafenib is an oral multiple tyrosine kinases inhibitor that suppresses angiogenesis and tumor-cell proliferation and augments the rate of apoptosis[13]. In the Sorafenib HCC Assessment Randomized Protocol (SHARP) study[14] and multicenter study in Asian-Pacific region[15], sorafenib was proved to be efficacious and safe to patients with advanced HCC. Nevertheless, subgroup analyses for macroscopic vascular invasion (MVI) in these two pivotal studies showed only a marginal survival benefit for sorafenib over placebo[16,17]. Therefore, there are still clinical unmet needs in the treatment of patients with HCC accompanying PVTT.

This article review recent data for the various treatment strategies for the patients with HCC accompanying PVTT.

SYSTEMIC THERAPY

HCC is relatively resistant to traditional chemotherapy and liver dysfunction complicates the use of chemotherapeutic agents that undergo hepatic metabolism[8,11]. Sorafenib, a multiple tyrosine kinases inhibitor that blocks tumor angiogenesis and tumor cell proliferation, was the 1st systemic agent proven to significantly increase survival in advanced-stage HCC in randomized controlled trials[14,15]. Sub-analyses of SHARP trial[17] identified 231 patients staged barcelona clinic liver cancer (BCLC) C due to MVI and demonstrated that the sorafenib group (n = 108) achieved a longer median overall survival (OS) (8.1 mo *vs* 4.9 mo) and time to progression (TTP) (4.1 mo *vs* 2.7 mo) than the control group (n = 123) received placebo. In the sub-group analyses of the Asia-Pacific trial[16], patients with MVI and/or extrahepatic spread who received sorafenib (n = 118) showed a better clinical outcome than in placebo group (n = 61): median OS (5.6 mo *vs* 4.1 mo), TTP (2.7 mo *vs* 1.3 mo) and disease control rate (30.5% *vs* 11.5%), respectively. Although the authors argued that the survival benefit with sorafenib was evident regardless of the presence of PVTT in those two pivotal studies, subgroup analyses for MVI showed only a marginal survival benefit of sorafenib over placebo.

LOCO-REGIONAL THERAPIES

TACE

Two key trials and a meta-analysis indicated that TACE can improve survival (median 19-20 mo compared to 16 mo for untreated patients in clinical trials) in intermediate-stage HCC[18-20]. However, PVTT is generally considered a contraindication for TACE because of concerns that interruption to hepatic arterial blood supply could result in an enormous segment of hepatic necrosis in patients whose blood supply is already compromised[8,12]. Nevertheless, there is evidence that selected patients with PVTT can tolerate a modified delivery of TACE provided they have good liver function and collateral blood flow around the obstructed portal vein[4,21]. Recent two studies reported improvements in survival compared to conservative care in HCC patients accompanying PVTT[22,23]. Luo *et al*[22] a performed a prospective nonrandomized study and reported significantly better survival with TACE (n = 84) compared

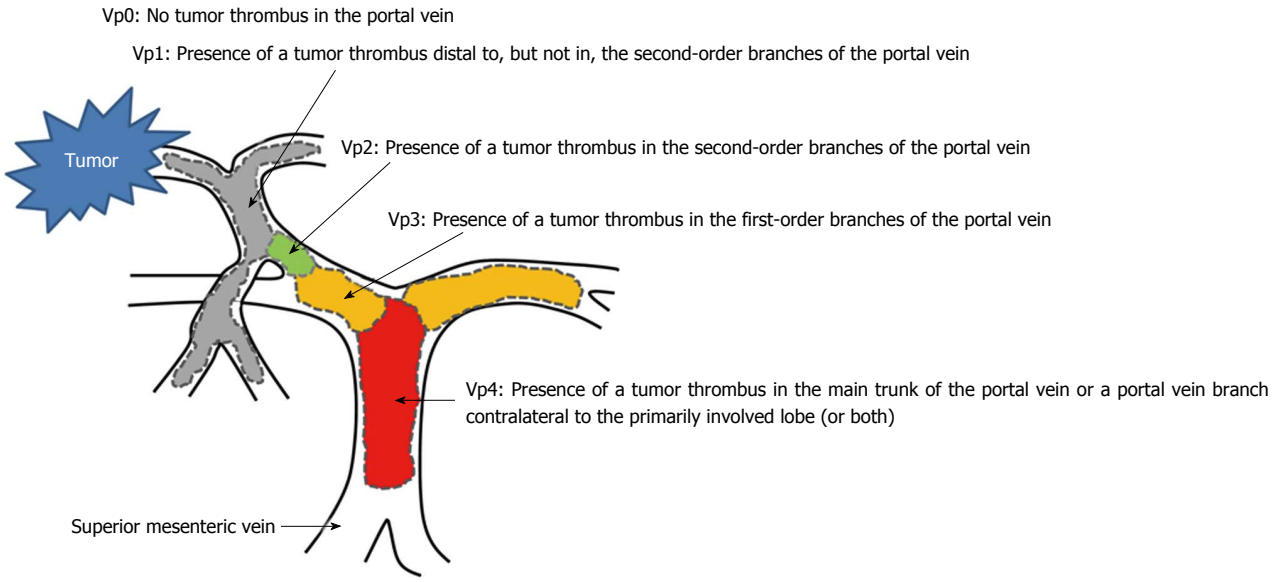

Figure 1 Classification for hepatocellular carcinoma with portal vein tumor thrombosis.

to conservative treatment (n = 80) either in non-cirrhotic or Child A cirrhotic HCC patients accompanying PVTT. The median OS, the 1-, and 2-year survival rates were 7.1 mo, 30.9%, and 9.2% for the TACE arm and 4.1 mo, 3.8%, and 0% for the conservative arm, respectively (P < 0.001)[22]. In the TACE group, the 40 patients with Vp1 or Vp2 survived longer than the 44 patients with Vp3 or Vp4 (median OS 10.2 mo *vs* 5.3 mo)[22]. In the second study, Chung *et al*[23] reported that TACE (n = 83) significantly improved survival compared to supportive care (n = 42; median OS 5.6 mo *vs* 2.2 mo, respectively; P < 0.001) in HCC patients with Vp4. Regardless of treatment (TACE or supportive care), patients with Child class B had worse outcomes (median OS 2.8 mo *vs* 1.9 mo) than those with Child class A (median OS 7.4 mo *vs* 2.6 mo)[23]. In addition, a recent meta-analysis evaluating 8 controlled trials (total 1601 HCC patients) demonstrated that TACE significantly improved the 6-mo (HR = 0.41; 95%CI: 0.32-0.53; P = 0.000) and 1-year (HR = 0.44; 95%CI: 0.34-0.57; P = 0.000) OS of HCC patients accompanying PVTT compared with best supportive treatment[24]. Moreover, another recent study comparing TACE and sorafenib in BCLC stage C HCC patients showed that TACE attained a comparable clinical outcome to sorafenib: the median OS was 9.2 mo (95%CI: 6.1-12.3 mo) for TACE group and 7.4 mo (95%CI: 5.6-9.2 mo) for sorafenib group (P = 0.377)[25]. The proportion of patients who had high-grade adverse events (grade $\geqslant$ 3) was significantly lower in the sorafenib arm (17%) than in the TACE arm (38%) (P = 0.024).

Drug-eluting bead TACE

TACE using DC Bead, drug-eluting microsphere (Biocompatibles UK Ltd, Farnham, United Kingdom), is a relatively novel modality related with favorable systemic doxorubicin exposure/toxicity and liver-specific toxicity compared to conventional TACE[26]. A recent study involving BCLC B HCC patients showed that DC Bead TACE resulted in a significantly better clinical outcome compared to conventional TACE[27]. However, Sellers *et al*[26] reported poor OS in HCC patients accompanying PVTT underwent DC Bead TACE. Further studies are warranted to evaluate the efficacy of DC Bead TACE and sorafenib in HCC patients accompanying PVTT.

Transarterial radioembolization

Transarterial radioembolization (TARE) is a form of catheter-directed, selective internal radiation therapy which delivers 25-32.5 μm sized microspheres loaded with high-energy radioisotope of yttrium-90 (^{90}Y), pure β-ray, into tumor tissue[28]. Tumoricidal radiation doses are delivered with minimal toxicity to functional liver parenchyma and minimal alteration in vascularity with TARE[29,30]. However, there is only microembolization (minimal to moderate embolization)[8,31]. Studies report improved median OS (7-41.6 mo) in BCLC B to C HCC patients following TARE and objective response rates (20%-77%)[32]. Although previous studies reported comparable efficacy for TARE and TACE in terms of tumor response and OS, patients receiving TARE tended to experience fewer complications and fewer days in hospital (typically 0-1.7 d with TARE compared to 1.8-6 d with TACE)[33-36], which are important quality-of-life considerations in patients with unresectable HCC.

Moreover, there is increasing evidence that TARE can be delivered safely and effectively in suitable HCC patients with PVTT, with several studies reporting median OS rates of approximately 10 mo following the procedure in these patients[34,37-42]. Again the extent of PVTT affected survival outcome. Salem *et al*[36] reported that the median OS for patients with Child class A (without extrahepatic spread) ranged from a median 16.6 mo for patients with branch involvement to 7.4 mo for those with Vp4. Median OS in patients accompanying PVTT and Child class B was only 5.6 mo. The risk of

Table 1 Clinical outcomes for hepatocellular carcinoma patients accompanying portal vein tumor thrombosis following surgical resection

Ref.	PVTT status[1]	No. of patients	Survival[2]		
			Median (mo)	1-yr (%)	3-yr (%)
Shi *et al*[49]	Vp2	139	NR	52.1	25.1
	Vp3	169		38.2	17.78
	Vp4	78		24.7	3.6
	Beyond Vp4	20		18.3	0
Lin *et al*[50]	Vp2				
	Vp3	63	NR	52.1	16
	Vp4	5		33.1	0
Chen *et al*[78]	Vp2-4	88	9	31.1	15.2
Matono *et al*[79]	Vp3-4	29	16.9	62.1	24.1

[1]Beyond Vp4 = extending to superior mesenteric vein; [2]Intrahepatic recurred lesions were treated by percutaneous ethanol injection therapy, radiofrequency ablation, transarterial chemoembolization, or systemic chemotherapy based on their hepatic functional reserve and the pattern of intrahepatic recurrence. NR: Not reported; PVTT: Portal vein tumor thrombosis.

death due to underlying liver disease rather than tumor progression becomes a factor in Child class B patients as evidenced by a median OS of only 7.7 mo in the total Child class B cohort despite a TTP of 8.4 mo[43]. Overall, the tolerability of TARE in patients with PVTT appeared to be comparable to that in those without PVTT[37,38,41,42]. When safety issues were specifically investigated, liver decompensation was not observed in the 2-mo period following TARE among HCC patients with PVTT[39], and clinical and laboratory adverse events in the 90-d period after TARE were not more frequent in BCLC C HCC patients than in BCLC A to B HCC patients[38]. Recently, Gramenzi *et al*[44] performed a cohort study directly comparing TARE and sorafenib in patients with intermediate-locally advanced HCC. Median OS of the two groups were comparable even after matching for independent prognostic factors including PVTT: sorafenib group (median OS: 13.1 mo; 95%CI: 1.2-25.9) and TARE group (median OS: 11.2 mo; 95%CI: 6.7-15.7).

Hepatic arterial infusion chemotherapy

The most studies regarding hepatic arterial infusion (HAI) used a combined regimen of cisplatin and 5-fluorouracil. The best results were reported by Ando *et al*[45]. The 5-year OS rate was 11.0% and the median OS was 10.2 mo in that study involving 48 patients treated with Vp2 to Vp4 by HAI with cisplatin plus 5-fluorouracil.

Radiofrequency ablation

In a small sample sized retrospective study (n = 13), radiofrequency ablation could ablaze both single intrahepatic medium-sized (3.7-5 cm) HCCs and the accompanying Vp4 with high efficacy and safety. The 3-year cumulative survival rate was 77%. There were no major adverse events. Mild ascites and elevated transaminase levels were observed in only three patients[46].

Percutaneous laser ablation

In a retrospective study, Lu *et al*[47] evaluated the application of percutaneous laser ablation as a treatment for PVTT in 108 patients and demonstrated that 3 years survival rate was 22.38%.

SURGICAL TREATMENTS

Most patients with HCC with Vp4 are considered technically unsuitable for curative resection, and the presence of PVTT is usually considered a contraindication for liver transplantation due to higher tumor recurrence rates[8]. Surgical resection in HCC patients accompanying PVTT is rare in Occidental area where the BCLC staging system which regards PVTT as a contraindication for surgery is endorsed[8]. However, throughout Oriental area, operation is considered a potentially curative treatment in suitable patients with PVTT as reflected in the consensus recommendations of Asia-Pacific Association for the Study of the Liver[11], although only about 10% of patients undergoing surgery have PVTT[48,49]. Surgical resection in these patients may improve portal venous pressure, liver function, quality of life and survival[8]. The range and position of PVTT significantly affect the potential clinical results following resection[8]. Previous studies have shown that HCC patients accompanying Vp2-Vp3 have better clinical outcomes after resection compared to those with Vp4 or beyond (Table 1)[48-50]. Surgical resection provided survival gains for patients with resectable HCC accompanying PVTT compared with TACE: the 1-, 3-, and 5-year OS rates were 42.0%, 14.1%, and 11.1% for the surgical group and 37.8%, 7.3%, and 0.5% for the TACE group, respectively (P < 0.001)[51]. A sub-group analysis by the PVTT type identified increased survival in the surgical group compared with the TACE group in patients accompanying type Ⅰ PVTT (Vp1-Vp2) or type Ⅱ PVTT (Vp3) (P < 0.001, P = 0.002, respectively)[51]. However, there were no significant differences in OS between the resection group and the TACE group for patients accompanying type Ⅲ PVTT (Vp4) and type Ⅳ PVTT (tumor thrombi involving the superior mesenteric vein) (P = 0.541, P = 0.371, respectively)[51]. In this study, after resection, there was only one postoperative in-hospital mortality caused by postoperative hepatic failure (0.5%), and the

major complication rate was 4.0% (8 of 201). If PVTT is not stick to the portal vein wall, total thrombectomy is possible. However, when the PVTT is adhered to the wall of the portal vein, there is a high chance of intramural invasion of HCC cells into the vessel wall on pathological examination after resection[52]. Therefore, in case of Vp4, the prognosis is extremely poor if the involved wall of portal vein is not resected. Although PVTT is generally considered a contraindication to liver transplantation, some centers have reported their positive results for transplant in the setting of gross vascular invasion. Xu *et al*[53] performed a study involving 24 patients undergoing liver transplantation for HCC accompanying PVTT (10 at main trunk, 10 at right branch, and 4 at left branch) and demonstrated a 6-mo, 1-year, and 2-year OS of 66.7%, 29.5%, and 23.6%, respectively.

EXTERNAL BEAM RADIOTHERAPY

Advances in technology, including three-dimensional conformal radiotherapy, proton beam radiotherapy and stereotactic body radiosurgery, have allowed selective delivery of increased radiation doses to tumors with minimal doses to normal tissue[54]. A number of mostly retrospective studies have examined the use of these new technologies in selected patients accompanying PVTT: median OS (6.7-11 mo), and 1-, 2-, and 5-year survival rates (30%-40%, 20%-30%, and 5.1%-24%, respectively)[55-61]. In a recent retrospective study assessing radiotherapy and surgical resection in 371 resectable HCC patients accompanying PVTT enrolled from two tertiary referral centers, the median OS was 12.3 mo for radiotherapy (n = 185) and 10.0 mo for resection (n = 186). The 1-, 2-, and 3-year OS were 51.6%, 28.4%, and 19.9% for radiotherapy group and 40.1%, 17.0%, and 13.6% for surgical group, respectively (P = 0.029)[62]. More recently, Nakazawa *et al*[63] did a retrospective study comparing the survival benefits of sorafenib *vs* radiotherapy in unresectable HCC patients accompanying PVTT (Vp3 or Vp4). Median OS did not differ significantly between the sorafenib and the radiotherapy group (4.3 mo *vs* 5.9 mo, respectively; P = 0.115)[63]. However, after propensity score matching (n = 28 per group), better median OS was noted in the radiotherapy than in the sorafenib group (10.9 mo *vs* 4.8 mo, respectively; P = 0.025)[63]. In the sorafenib group, 90% (25 of 28) patients permanently discontinued sorafenib owing to disease progression (n = 10) or adverse events (n = 15). However, there was no high-grade (grade $\geqslant$ 3) gastrointestinal or hepatic toxicity in the radiotherapy group. Future large scale prospective studies are warranted to approve the results of these retrospective studies.

COMBINATION STRATEGIES

TACE combined with sorafenib

Zhu *et al*[64] conducted a retrospective study comparing the efficacy and safety of TACE plus sorafenib in 91 HCC patients accompanying PVTT (46 TACE-sorafenib *vs* 45 TACE alone). TACE plus sorafenib showed significant survival benefits over TACE alone in patients with Vp3 (median OS, 13 mo *vs* 6 mo; P = 0.002) or Vp1-2 (median OS, 15 mo *vs* 10 mo; P = 0.003). However, the control arm of this study was TACE alone instead of sorafenib alone. A randomized, controlled phase Ⅲ trial of sorafenib with or without conventional TACE in patients with advanced HCC is recruiting participants (NCT01829035). The result of this study is awaited to answer whether TACE, as a powerful complimentary armament for sorafenib, could be allowed for HCC patients accompanying PVTT.

TACE combined with radiotherapy

The recent advances with a co-treatment modality of TACE combined with radiotherapy have demonstrated superior results over TACE alone[65]. In addition, the survival benefit has been reported in patients accompanying PVTT who have been treated with TACE plus radiotherapy[66-68]. Recently, Cho *et al*[69] conducted a retrospective study comparing TACE combined with radiotherapy (n = 67) with sorafenib (n = 49) in 116 patients accompanying PVTT and demonstrated that OS in the TACE plus radiotherapy group was significantly prolonged over the sorafenib group (14.1 mo *vs* 3.3 mo, P < 0.001). Even in the matched cohort by propensity score, the TACE combined with radiotherapy group demonstrated extended OS over the sorafenib group (6.7 mo *vs* 3.1 mo, P < 0.001)[69].

Surgical resection combined with multimodal treatments

There have been several studies of surgical resection-based multimodality treatment including surgical resection after TACE; surgical resection followed by TACE, HAI, and portal vein infusion chemotherapy; ^{90}Y plus doxorubicin or preoperative intravenous chemotherapy with doxorubicin, cisplatin and 5-fluorouracil plus subcutaneous interferon-α (PIAF); postoperative percutaneous isolated hepatic perfusion; surgical resection followed by interferon with 5-fluorouracil; and surgical resection after radiotherapy. The median OS after surgical resection-based multidisciplinary treatments ranged from 13.0 to 22.1 mo, implying that multimodality therapy contributed to prolonged long-term survival[70-77]. In a controlled trial by Peng *et al*[77], 126 HCC patients accompanying PVTT (Vp3-4) were randomized into TACE after surgical resection (TACE group) or surgical resection alone (control group). The median OS was better in the TACE group (13 mo) than in the control group (9 mo). The estimated survival rates for 1-, 3-, and 5 years were significantly improved in the TACE group (50.9%, 33.8%, and 21.5%; respectively) than in the control group (33.3%, 17.0%, and 8.5%, respectively; P = 0.0094). The available evidence shows that surgical resection-based multimodality treatments are effective and should be estimated in further trials.

Table 2 Comparing various treatment strategies for hepatocellular carcinoma patients accompanying portal vein tumor thrombosis

	Indication	Advantages	Disadvantages
Sorafenib	BCLC stage C	Showing survival benefit in infiltrative type HCC	Modest efficacy compared to placebo control Hand-foot skin reaction
TACE	Nodular type HCC up to Vp4 Child A liver function	Wide indication	Post TACE syndrome Potential risk of liver failure
TARE	Tumor extension ≤ 50% of liver volume Unilobar Nodular type Up to Vp4	Down-staging allowing liver transplantation	Requiring additional lung shunt study due to the risk of lung injury
RFA	Single medium-sized HCCs (3-5 cm)	Less invasive	If the intraparenchymal tumor was not completely ablated by RFA, complete effects on the thrombus probably would not be produced
Surgery	Up to Vp4 Single medium-sized HCCs (≤ 7 cm) Up to Vp4 No HV/IVC invasion	Less expensive technic Better outcomes than other patients with HCC who are BCLC stage C with Child A liver function	Invasive and expensive technic Potential risk of liver failure
External beam radiotherapy	AFP ≤ 30 ng/mL Tumor extension ≤ 60% of liver volume	Combined to multimodal strategies	Potential risk of radiation induced liver disease Potential risk of GI tract toxicities

BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; RFA: Radiofrequency ablation; HV: Hepatic vein; IVC: Inferior vena cava; AFP: Alpha-fetoprotein; GI: Gastrointestinal.

INDIVIDUALIZED TREATMENT PLANS FOR DIFFERENT PATIENTS

For HCC patients accompanying PVTT with Child class B, portal hypertension, or Eastern Cooperative Oncology Group (ECOG) 2, sorafenib would be best option as recommended in BCLC guideline. For HCC patients accompanying PVTT with Child class C, portal hypertension, or ECOG > 2, we have to treat these patients with best supportive care. For HCC patients accompanying PVTT with Child class A, no portal hypertension, and ECOG 0-1, we could treat these patients with individualized treatment plans, as follows: (1) Single HCC (≤ 2cm) with PVTT: In this setting, we could consider surgical resection as best options other than sorafenib. Alternatively, TACE and external beam radiotherapy (EBRT) could be other good options; (2) Single HCC (> 2 cm) with PVTT: For single HCC larger than 2 cm with PVTT, we still consider surgical resection as best option for patients with resectable tumor, reserved hepatic function and sufficient post-operative remnant hepatic volume. If tumor size is 10 cm or less, TACE and EBRT could be alternative options. For single huge HCC larger than 10 cm with PVTT, sorafenib would be 1st line option; (3) Multiple (maximal tumor size ≤ 2 cm) with PVTT: If maximal tumor size is 2 cm or less, we could adopt TACE as best option for multiple HCC. Sorafenib would be another best option for these patients; and (4) Multiple (maximal tumor size > 2 cm) with PVTT: In this setting, sorafenib would be 1st line option. However, we could still consider TACE as alternative option if maximal tumor size is 10 cm or less and tumor extent ≤ 50% of liver volume.

CONCLUSION

Although direct appraisals of the clinical outcomes of treatment are inappropriate by the differences in the patients' baseline characteristics (Table 2), in HCC patients accompanying PVTT, evidence from retrospective and prospective studies suggests that multidisciplinary approaches including TACE and/or radiotherapy, TARE, and surgical resection-based multimodal treatments in selected patients may provide better outcomes than sorafenib. For resectable single nodular HCC patients with PVTT, we could treat these patients with surgical resection as 1st line treatment if they have Child class A, no portal hypertension, and ECOG 0-1. TACE, EBRT, and sorafenib would be alternative treatment options for these patients. For multi-nodular HCC patients accompanying PVTT, we could treat these patients with TACE or sorafenib if they have Child class A, no portal hypertension, and ECOG 0-1. TACE would be 1st line if maximal tumor size is 2 cm or less and sorafenib would be 1st line if maximal tumor size is greater than 2 cm. For HCC patients accompanying PVTT with Child class B, portal hypertension, or ECOG 2, sorafenib would be best option. However, for HCC patients accompanying PVTT with Child class C, portal hypertension, or ECOG > 2, we should treat these patients with best supportive care as recommended in BCLC guideline. Given the modest survival gain of sorafenib, surgical resection-based multimodal treatments for resectable HCC accompanying PVTT and TACE-based appropriate combined therapies for unresectable HCC accompanying PVTT may enhance the clinical outcomes of HCC patients with PVTT.

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