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Review

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New perspectives on the management of hepatocellular carcinoma with portal vein thrombosis

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Despite advances in the treatment of hepatocellular carcinoma (HCC), managing HCC with portal vein thrombosis (PVT) remains challenging. PVT is present in 10-40% of HCC cases at the time of diagnosis and its therapeutic options are very limited. Current guidelines mainly recommend sorafenib for advanced HCC with PVT, but surgery, transarterial chemoemolization, external radiation therapy, radioembolization, transarterial infusion chemotherapy, and combination therapy are also still used. Furthermore, several new emerging therapies such as the administration of immunotherapeutic agents and oncolytic viruses are under investigation. This comprehensive literature review presents current and future management options with their relative advantages and disadvantages and summary data on overall survival. **(Clin Mol Hepatol 2015;21:115-121)**

Keywords: Management; Hepatocellular carcinoma; Portal vein thrombosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer, and the third most common cause of cancer-related death worldwide.[1] It is responsible for over 600,000 deaths annually.[2] When patients with HCC have been detected early, curative treatment such as resection and percutaneous ablation are feasible. However, approximately 10-40% patients with HCC have portal vein thrombosis (PVT) at the time of diagnosis.[3,4] Overall survival have been reported to be much shorter in patients with PVT, compared to patients without PVT, because these patients have more chances to have metastatic disease at diagnosis and fewer therapeutic options. Reported overall survival ranged from 2-4 months in patients with PVT treated with supportive care, compared to 10-24 months in HCC patients without PVT.[4,5] If thrombus involved the main portal vein, the prognosis would be much worse than in case of thrombus involving a branch portal vein.[6]

For decisions regarding initial treatments, the Barcelona Clinic Liver Cancer (BCLC) staging system from Western guidelines is frequently applied.[7,8] In this system, management options for HCC with PVT are more limited than for HCC without PVT. As three-quarters of HCC cases occur in East Asia, the experiences and data in this area should have been substantially accumulated, so this article aim to review the current status and future prospect of the management of HCC with PVT (Table 1).

SURGICAL MANAGEMENT

Liver resection produces the best prognosis when it involves

Abbreviations:

BCLC, Barcelona Clinic Liver Cancer; HAIC, Hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; RCT, randomized controlled trial; TACE, Transarterial chemoembolization; TTP, time to progression; VEGFRs, Vascular endothelial growth factor receptors; 90Y, yttrium-90

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Table 1. Summary of management for hepatocellular carcinoma with portal vein thrombosis

	Survival data (months)			Adverse events
	Overall survival	Main PVTT	Branch PVTT	
Supportive care[5]	2-4			
Surgical resection[6]	9-33	9-10		Operative mortality; 0-6%
TACE[23]	7-10			Liver failure, postembolization syndrome
External radiation therapy[26]	9.2			Radiation induced liver disease
HAIC[42,43]	6-7			
Radioembolization[33-35]	10	4.5	16	Fatigue, hyperbilirubinemia, GI ulceration
Sorafenib[44,46]	6-8			Skin reaction, diarrhea, fatigue

HAIC, hepatic artery infusion chemotherapy; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; GI, gastrointestinal.

only one or two small tumors. Surgical resection for PVT generally resulted in poorer outcomes. Surgical resection for HCC with PVT is more frequently employed across Asia.[9] Overall median survival for patients with portal vein invasion ranged from 9 to 33 months according to the degree of portal vein invasion.[6] In a study of 438 PVT patients who underwent resection for PVT,[10] overall survival was 18.8 months with branch portal invasion and 10.1 months with main portal invasion. In general, outcomes of surgical resection for tumors involving the main portal vein remain relatively poor (median survival, 9-10 months; and 3-year survival rates, 0-6%).[10] The main problem of liver resection is that it is often technically infeasible in patients with PVT. The operative mortality rates is 0-6%.

TRANSARTERIAL CHEMOEMBOLIZATION

Transarterial chemoembolization (TACE) is widely used as a first-line treatment for unresectable HCC[11-13] and is recommended for patients with BCLC stage B, multinodular asymptomatic tumors, and without vascular invasion or extrahepatic spread. A study of the survival benefits of TACE found that the survival time was longer for intermediate-stage patients (BCLC stage B) treated with TACE (median survival, 19–20 months) than for untreated intermediate-stage controls (median survival, 16 months).[14,15]

Indications for TACE are the absence of vascular invasion and extrahepatic spread, a preserved underlying liver function (mostly Child-Pugh class A or B7 without ascites), and asymptomatic multinodular tumors.[16,17] Since performing TACE on patients with portal vein invasion or advanced liver failure causes serious complications due to ischemic events in the liver, chemoembolization is not recommended for the patients with decompensated liver cirrhosis, advanced liver dysfunction (Child-Pugh class C), macroscopic invasion, and extrahepatic spread.

However, in some patients with compensated liver function, TACE can be performed safely with superselective method and is associated with improved overall survival compared to supportive care.[18-20] In recent two large meta-analysis.[21,22] TACE was favored over supportive care for HCC with main as well as branch portal vein tumor thrombus. Overall survival among PVT patients treated with TACE in these studies ranged from 7.0 to 10.2 months. Notably, median survival after TACE prolonged as much as 22-30 months when a tumor is nodular and restricted to 1 lobe or 1-2 segments and hepatic function is preserved, even in the presence of main portal vein tumor thrombosis.[23]

Therefore, TACE is considered to be a one of therapeutic option for selected patients with PVT, if their underlying liver function is favorable and the procedure is technically possible. However, reported overall survival of 7.4 to 10.2 months is not significantly better than systemic sorafenib.

EXTERNAL RADIATION THERAPY

External radiation therapy for liver lesions has not been broadly performed in patients with compromised underlying liver function due to risk of radiation-induced liver disease.[24] However, with advanced of newer techniques, in the form of stereotactic body radiation therapy, high doses of radiation can be delivered very selectively, with relative sparing of non-tumorous liver parenchyma.[25]

The effect of external radiation therapy in HCC with PVT has not been well studied and the use of external radiation therapy for HCC is not yet regarded as standard treatment, but remains an area of active investigation. The median survival was shown to be 9.2 months in a large multicenter study in Korea of 994 HCC patients with portal vein tumor thrombosis.[26] Studies from Japan

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and China also reported that overall survival in patients receiving radiotherapy was 10.9 months and 12.3 months and it is significantly better than in patients receiving sorafenib (4.8 months, P=0.025) or undergoing surgery (10.3 months, P=0.029).[27,28] In other studies, when external radiation therapy is combined with other modalities such as sorafenib or TACE , overall survival was reported to be 10 months or more.[29,30] Although these data of radiotherapy in advanced HCC, radiotherapy has not been incorporated into the international guidelines for HCC because of lack of prospective randomized trial. Therefore, there are urgent needs for well-designed randomized controlled studies.

RADIOEMBOLIZATION

Radioembolization involves injection of ^{131}I-labeld lipiodol[31] or glass microspheres containing an isotope into the hepatic artery. The most widely used istotope is yttrium-90 (90Y),[32-34] it emits pure, high-energy β particles, has a half-life of 2.67 days, and an average penetration power of 2.5 mm (maximum, 11 mm). Resin or glass microspheres with a diameter of 35 μm are used to transport the 90Y. The injected microspheres minimize the thrombotic effect in the artery and are distributed in high concentrations in hypervascular HCC tumors, displaying a radiation-induced antitumor effect. Nuclear medical examination using technetium-99m microaggregated albumin is required in advance of the radioembolization procedure to determine the treatment locations, the required dose of radiation, and measure the risk and degree of exposure to organs other than the target (i.e., the liver).

90Y has been mainly studied as a locoregional therapy for unresectable HCC that is not amenable to TACE because of diffuse or multifocal disease, or as an alternative to TACE.[6] The efficacy of 90Y in patients with HCC who had PVT could be found in subgroup analysis from the three largest series of HCC patients treated with 90Y. In these series, patients who had PVT demonstrated remarkably similar overall survival times ranging from 10.0 to 10.4 months among all patients with PVT.[33-35] One of these studies reported that overall survival was 16.6 months among Child-Pugh A cirrhotics with branch PVT and it was decreased to 4.5 months among Child-B cirrhotics with main PVT. Smaller series of patients with PVT treated with 90Y have reported overall survival ranging from 7.2 to 13 months.[36] In another small nonrandomized study, among patients with major vascular invasion, the 90Y group showed an overall survival of 12.0 months, compared to 8.0 months in the TACE group.

In addition, in term of safety, patients receiving radioembolization needed less hospitalization and fewer treatments. Fewer treatment sessions should improve quality of life and reduce the possibility of liver derangement; therefore, in these respects, radioembolization is considered better than conventional TACE and another option for patients with PVT.

CYTOTOXIC CHEMOTHERAPY

Cytotoxic chemotherapy has known to be not effective through most clinical trials to date.[37,38] It is because delayed metabolism of chemotherapeutic agents in the presence of liver cirrhosis may enhance their toxicity and HCC is relatively chemo-resistant to most cytotoxic anticancer drugs.[39] Instead, Hepatic arterial infusion chemotherapy (HAIC) has been investigated for treatment of advanced HCC with portal vein tumor thrombosis in Asian countries.[40,41] In HAIC, chemotherapeutic agent is infused into the hepatic artery *via* an implanted catheter, which reduces systemic side effects by first pass effects and maximizes drug delivery to the tumor. Furthermore, HAIC does not use embolic material, therefore the presence of tumor thrombus may not aggravate ischemic injuries after TACE. In clinical data on HAIC, low dose or high dose of cisplatin and 5- fluorouracil was mainly used as chemotherapeutic agents and the effect of HAIC was compared to systemic chemotherapy or supportive care or sorafenib. In those studies, HAIC showed survival benefit compared to other treatments modalities (median survival 6-7 months versus 5.5, 4 and 2 months in sorafenib, systemic chemotherapy and supportive care, respectively).[42,43] Although there are no well-designed prospective studies to demonstrate these results, HAIC can be an alternative therapy for patients with portal vein tumor thrombosis, especially in case that patients with advanced HCC do not respond or are intolerant to standard therapy.

MOLECULAR TARGET THERAPY

Sorafenib is the multi-tyrosine-kinase inhibitor that targets vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, and the Raf-1 and c-kit receptors. Sorafenib was the first ever molecularly targeted agent confirmed for the treatment of HCC. In a phase III, multicenter, randomized controlled trial (RCT) conducted on a Western population,[44] the median survival period of patients with progressive HCC with he-

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patic portal invasion and extrahepatic spread who were treated with sorafenib was 10.7 months, which was significantly higher than the median survival period (7.9 months) of the control group, who were treated with palliative medicine alone (P=0.00058). In this study, sorafenib also prolonged the time to tumor progression (TTP; 5.5 months and 2.8 months for the sorafenib-treated and control groups, respectively). In a subgroup analysis,[45] patients with macroscopic vascular invasion, presumably largely consisting of PVT, had an overall survival of 8.1 months in the sorafenib group, compared to 4.9 in the control group. The respective times to progression were 4.1 and 2.7 months. In a phase III, RCT conducted in Pacific Asia by the Asian Pacific Association for the Study of the Liver, the median survival period of patients with progressive HCC who were treated with sorafenib was 6.5 months, which was again significantly higher than that of the control group (4.2 months; hazard ratio, 0.68; 95% confidence interval, 0.50–0.93; P=0.014).[46] In subgroup analyses,[47] sorafenib was found to have modestly prolonged survival in patients with macroscopic vascular invasion and/or extrahepatic spread of tumor (5.6 months *vs* 4.1 months). TTP was likewise somewhat prolonged (2.7 months *vs.* 1.2 months). The most frequent adverse reactions to sorafenib are hand-foot skin reaction, diarrhea, and fatigue, which occur during the treatment in 40% of patients and it may necessitate dose reduction or discontinuation in a minority of patients.

Sorafenib is considered as a standard treatment for patients with unresectable HCC whose liver function was well-compensated (Child-Pugh A). Several studies reported that a portion of Child-Pugh B also may show survival benefit from sorafenib treatment.[48]

The main problem of sorafenib is that, although a select group of patients showed excellent response to sorafenib,[49,50] the majority of patients with PVT have shown just modest response and survival. Therefore, there are continued efforts to improve the efficacy of sorafenib. First, combination of sorafenib with locoregional therapies remains an area of active investigation. Second, newer agents were evaluated in clinical trials.

COMBINATION THERAPY

Sorafenib combined with TACE

In studies comparing TACE plus sorafenib and sorafenib alone, overall survival and time to progression (TTP) was significantly longer in combination group than sorafenib alone group (median survival, 8.9 and 5.9 months, respectively; P=0.009) (TTP, 2.5 and 2.1 months, respectively; P=0.008).[51] Another study also showed that the efficacy of TACE plus sorafenib is more superior than TACE alone in advanced stage HCC patients in terms of overall survival and TTP (overall survival, 7.0 and 4.9 months, respectively; P=0.003) (TTP, 2.6 and 1.9 mo, respectively; P=0.001).[52] A phase Ⅱ study which combined drug eluting bead TACE with sorafenib showed objective response rate of 58% and disease control rate of 100% in advanced HCC patients.[53] These data showed that the combination is a promising HCC treatment strategy, but its benefits compared with monotherapy needs to be confirmed in a prospective randomized trial.

Sorafenib combined with radiotherapy

The combination treatment using sorafenib and radiotherapy are thought to be synergistic because in vitro and in vivo experiment showed sorafenib enhance the radiosensitivity of human HCC cell lines by inhibiting radiation-induced activation of vascular endothelial growth factor receptors (VEGFRs), a downstream kinase (extracellular signal regulated kinase), and nuclear factor-κB and by increasing radiation-induced apoptosis.[54] In a multicenter phase Ⅱ study in which sorafenib was administered after radioembolization, the median overall survival time was 8.6 months in patients with advanced stage HCC[55] Considering the median survival of phase Ⅲ Asian- Pacific trial data of sorafenib was 6.5 months in advanced HCC, the data of radioembolization plus sorafenib combination therapy seems to be favorable.[46] About data of sorafenib plus external beam radiation, a phase Ⅱ study of sorafenib therapy plus external beam radiation reported an initial complete or partial response rate of 55% and a 2-year overall survival rate of 32% in 40 Taiwanese patients with advanced HCC.[56] These results are promising but further research would be needed.

Emerging therapy

Besides sorafenib, several newer molecular target agents are investigated but so far none of these drug such as sunitinib, brivanib, linifanib, or the combination of sorafenib and erlotinib have demonstrated efficacy in phase III trials, either in the setting of progression on sorafenib or as primary therapy.[57] However, recent two trials showed encouraging results in subgroup analysis. In a phase 2 study about tivanitinib, MET inhibitor, progression free survival was significantly improved compared to placebo

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(Hazard radio, 0.64, 90% confidence interval, 0.43-0.94; *P*=0.04) and patients with high MET expression had showed substantial benefit from tivanitinib in terms of median overall survival (7.2 months vs. 3.8 months, *P*=0.01).[58] Furthermore, in a phase 3 trial of the vascular endothelial growth factor receptor-2 antibody, ramucirumab, median survival was significantly improved in patients with baseline alpha-fetoprotein more than 400 ng/mL. The efficacy of these agents will be investigated in further study.

Moreover, immunotherapeutic agent such as checkpoint inhibitor (CTLA-4 antibody, programmed cell death receptor-1 blocking antibody) and oncolytic viruses are another promising agent because HCC showed immunologic response spontaneously or to adoptive immunotherapy. Phase I trial (NCT01853618) for tremelimumab (CTLA-4 antibody) and phase I/2 trial (NCT01658878) for nivolumab (programmed cell death receptor-1 blocking antibody) are currently undertaken. Oncolytic viruses are also promising agent because these viruses preferentially replicated in cancer cells as well as final kill the cancer cells.[59] In HCC, several oncolytic viruses have been investigated and JX-594 is currently leading agent among these viruses.[60] JX-594 is a genetically engineered vaccinia virus and its action mechanism is to induce virus replication-dependent lysis of tumor cells as well as to induce tumor specific immunity. In phase 2 clinical trial of JX-594, high dose of JX-594 showed overall survival about 14.1 months in advanced HCC.[61] Further study of this virus are under investigation in advanced HCC.

CONCLUSIONS

Despite recent progress in the treatments for HCC, treatment for patients with PVT remain still as challenging area. Current clinical guideline recommend sorafenib only. However, besides sorafenib, various therapies including surgery, TACE, external radiation therapy, HAIC and radioembolizaiton may be management options in selected patients and the usefulness of combination treatment need to be verified. Newer therapeutic options such as such as immunotherapeutic agent and oncolytic virus are under investigation.

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Conflicts of Interest

The authors have no conflicts to disclose.

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