RESEARCH ARTICLE

Trends in treatment for hepatocellular carcinoma in Japan

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Abstract

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer deaths in Japan, and it has gradually decreased in the last quarter century. The reason for the decrease in HCC patients is the decrease of patients with hepatitis C virus due to avoiding unnecessary blood transfusions and development of direct-acting antiviral agents (DAAs), which have been available since 2014, along with interferon and oral antiviral agents in Japan. On the other hand, the numbers of HCC patients with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) are increasing. In the treatment strategy for HCC in the Japanese guideline, the algorithm involves five clinicopathological factors: liver function (assessed using the Child-Pugh classification, liver damage score, and the ICG-R15 value), presence of extrahepatic metastases, presence of vascular invasion, number of tumors (within 3 or more than 4), and tumor size (within 3 cm or over 3 cm). Surgical resection is sometimes indicated for extrahepatic metastases in patients with well-controlled intrahepatic HCC, and for advanced HCC with vascular invasion, hepatectomy is also recommended as one of the treatment options according to the results of a nationwide survey in Japan. In the latest Japanese guideline, the recommended chemotherapy for advanced HCC is lenvatinib or sorafenib as first-line and regorafenib as second-line therapy. Currently, based on the results of various clinical trials for advanced HCC, the therapeutic options for advanced HCC have increased, such as combination therapy of atezolizumab and bevacizumab, ramucirumab, and cabozantinib. Reports of conversion surgery after chemotherapy have also increased, and the development of multidisciplinary treatment for advanced HCC will be of further interest in the future.

Keywords: Hepatocellular carcinoma, Japanese guideline, multidisciplinary treatment

Introduction

The incidence of hepatocellular carcinoma (HCC) in Japan has decreased gradually in the last quarter century. In the 1990s, 70% of patients with HCC had chronic hepatitis C, and 15% of them had chronic hepatitis B. Today, the proportion of patients with chronic hepatitis C has decreased to 50%, while that with non-B non-C chronic liver disease has increased to 20%. In particular, the numbers of patients with non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) are increasing. The decrease in the number of patients with hepatitis C virus is probably due to avoiding unnecessary blood transfusions and development of direct-acting antiviral agents (DAAs), which have been available since 2014, along with interferon and oral antiviral agents in Japan. Hepatocellular carcinoma was the fourth leading cause of cancer deaths in Japan in 2010, but it was the fifth in 2018 [1].

Comparison of the treatment strategies for HCC between the Japanese guideline and BCLC system.

The algorithm of the treatment strategy for HCC in the Japanese guideline for HCC 2017 [2] involves five clinicopathological factors: liver function, presence of extrahepatic metastases, presence of vascular invasion, number of tumors, and tumor size (Fig1). Liver function can be assessed using the Child-Pugh classification, liver damage score, and the ICG-R15 value as a criterion for safe hepatectomy. Comparison of the treatment strategies for HCC between Japanese guideline 2017 and BCLC staging system [3] is shown on table 1. Briefly, if the tumor number is 3 or less and the tumor size is 3cm or less in patients with good or moderate liver function (Child-Pugh A or B), hepatectomy, radiofrequency ablation (RFA) and liver transplantation (for patients with poor liver function in Japanese guideline) are recommended in both criteria. But which is better hepatectomy or RFA? In a multicenter, phase III, randomized, controlled trial comparing these two treatments (hepatectomy: n=150, RFA: n=151), the SURF Trial [4], the 3-year recurrence-free survival rate was 49.8% in the hepatectomy group and 47.7% in the RFA group. There was no significant difference in recurrence-free survival between the two treatments (p= 0.793). Further analysis of the overall survival of the patients is scheduled in 2021, and we have not reached any conclusion on the best local treatment option for localized HCC.

Table 1: Comparison of Japanese guideline and BCLC staging system for treatment strategy for HCC

	Recommended treatment	
	Japanese guideline	BCLC staging system
Very early stage (BCLC 0) ● Single ≤2cm ● Preserved liver function ● PS 0	Liver resection Ablation	
Early stage (BCLC A) ● Single or up to 3 nodules ● ≤3cm ● Preserved liver function ● PS 0	● Good or moderate liver function →Liver resection Ablation ● Poor liver function and within transplantation criteria →Transplantation	● Solitary →Liver resection Ablation Transplantation ● 2-3 nodules ≤3cm →Ablation Transplantation
Intermediate stage (BCLC B) ● Multinodular ● Preserved liver function ● PS 0	● 2-3 nodules, 3cm< →Liver resection ● 4 or more nodules →TACE, HAIC, systemic therapy	TACE
Advanced stage (BCLC C) ● Portal invasion ● Extrahepatic spread ● Preserved liver function ● PS 1-2	● Extrahepatic spread →Systemic therapy ● Vascular invasion →Systemic therapy Liver resection TACE HAIC	Systemic therapy
Terminal stage (BCLC stage D) ● End stage liver function ● Not transplantable ● PS 3-4	BSC	

BCLC: Barcelona clinic liver cancer, HAIC: Hepatic artery infusion chemotherapy
PS: Performance status, TACE: Transcatheter arterial chemoembolization,

In patients with intermediate stage, the treatment strategy has much difference between the two guidelines. If the tumor number is 3 or less, and the tumor size is 3 cm or greater in patients with good liver function, hepatectomy is recommended in Japanese guideline [5-7], while transcatheter arterial chemoembolization (TACE) is recommended in BCLC system. In patients with tumors larger than 3cm surgical resection and hepatic arterial infusion chemotherapy (HAIC) remain the therapeutic options in Japanese guideline [8.9], while they are not recommended and systemic chemotherapy is recommended as palliative treatments in BCLC system.

In patients with advanced HCC, systemic chemotherapy using molecular targeted agents would be the important option for the control of the disease in both criteria. However, in Japanese guideline, hepatectomy is recommend as one of the treatment options even for patients with HCC having vascular invasion, which is abandoned in BCLC system. This Japanese aggressive recommendation is based on the results of a retrospective analysis of patients with portal vein or hepatic vein tumor thrombus undergoing aggressive surgical resection and having longer overall survivals than patients without surgical resection [10.11]. HAIC is one of the treatment options for advanced HCC with vascular invasion in Japanese guideline. Better prognosis in the patients with macrovascular invasion treated with HAIC than in the patients treated with sorafenib was reported [12]. In addition, surgical resection is sometimes added in patients with pulmonary metastases, adrenal metastases, lymph node metastases, and peritoneal dissemination in patients with well-controlled intrahepatic HCC.

Indications for liver transplantation are somewhat different in the two guidelines. In Japanese guideline, liver transplantation for HCC is indicated mainly in patients with poor or end stage liver function within the Milan criteria or within the 5-5-500 criteria (tumor size within 5 cm, number of tumors within 5, and serum AFP value less than 500 ng/ml) [13]. In BCLC system, liver transplantation can be indicated in patients with preserved liver function. This discrepancy could be explained by the difference of the liver donation in Japan and western countries, that is living donor transplantation is extremely dominant, but diseased donor transplantation is scarce in Japan. In addition, surgical resection for HCC remains the best therapeutic option in Japan, promising approximately 50% of 5-year survival rates.

Table 2: The clinical trials of molecular therapy and immunotherapy for HCC

Trial	year	journal	disease	treatment	n	Median-OS (months)	P value
SHARP	2008	N Eng J Med	Advanced	SOR	299	10.7	<0.0001
				Placebo	303	7.9	
RESORCE	2017	Lancet	SOR failure	Rego	379	10.6	<0.0001
				Placebo	194	7.8	
REFLECT	2018	Lancet	BCLC stage BC	LEN	478	13.6	ND
				SOR	476	12.3	
REACH-II	2019	Lancet Oncol	BCLC stage BC	Ram	197	8.5	0.0199
				Placebo	95	7.3	
CELESTIAL	2018	N Eng J Med	Advanced	Cabo	470	10.2	0.005
				Placebo	237	8.0	
IMbrave 150	2020	N Eng J Med	unresectable	Atez+Bev	336	6.8(PFS)	<0.001
				SOR	165	4.3(PFS)	

Atez: Atezolizumab

BCLC: Barcelona clinic liver cancer

Bev: bevacizumab

Cabo: cabozantinib

LEN: lenvatinib

OS: overall survival

PFS: progression free survival

SOR: sorafenib

Rego: regorafenib

Ram: ramcirumab

Chemotherapy for advanced HCC

Advances in the chemotherapy for HCC in the last two decades have been outstanding. The results of randomized, controlled trials of chemotherapeutic treatments for advanced HCC are shown in Table 2. The SHARP trial [14] showed significant prolongation of survival of patients with unresectable advanced HCC, using sorafenib, a molecular target drug. The RESORCE trial [15] showed the significant impact of regorafenib as a second-line treatment after sorafenib for advanced HCC, and the REFLECT trial [16] showed non-inferiority of lenvatinib to sorafenib. In the

Japanese guideline, sorafenib or lenvatinib is recommended in the first-line, and regorafenib is recommended in the second-line for the treatment of patients with advanced HCC and good performance status and liver function. The REACH-II trial showed that ramucirumab can be recommended as the second-line treatment option following sorafenib for HCC with an AFP value of 400 ng/ml or higher [17]. Although it is not yet included in the Japanese guidelines 2017, ramucirumab is indicated as a second-line therapy after sorafenib treatment in Japanese clinical practice. The CELESTIAL trial showed that cabozantinib, which was not approved in Japan until 2020, is also recommended as a second-line treatment after sorafenib [18]. In the field of immunotherapy, the IMbrave 150 trial [19] showed that the combination of atezolizumab, a PD-L1 antibody, and bevacizumab, an angiogenesis inhibitor, was superior to sorafenib monotherapy (6-month survival rate: 84.8% vs. 72.2%, HR = 0.58, $p < 0.05$). Currently, combination therapy of atezolizumab and bevacizumab would be recommended as the first-line treatment, sorafenib or lenvatinib as the second-line, and regorafenib, ramucirumab, or cabozantinib as the third-line treatments for advanced unresectable HCC. The therapeutic options for advanced HCC have increased in the last two decades, and the development of multidisciplinary treatment such as conversion surgery for initially unresectable HCC is expected in the future [20].

Conclusion

HCC is one of the cancers with a poor prognosis, but recent developments in chemotherapy have been remarkable. The results of future clinical trials of chemotherapy and multidisciplinary treatment combined with surgical resection, RFA, and TACE will be of further interest.

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