Commentary

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Adjuvant systemic drug therapy and recurrence of hepatocellular carcinoma following curative resection

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ABSTRACT: Postoperative recurrence of hepatocellular carcinoma (HCC) has a negative impact on long-term survival. According to available evidence, many systemic untargeted agents are ineffective as adjuvant therapy to prevent the recurrence of HCC following curative resection. Interferon α has potential effectiveness as adjuvant therapy for HCC in the presence of underlying conditions such as HBV or HCV infection. Oral polyprenoic acid has also proven its effectiveness according to a prospective study; however, no other studies have reported polyprenoicacid (acyclic retinoid) to be effective. Sorafenib is the only systemic molecular targeted agent that has proven effectiveness as adjuvant therapy according to a pilot study. To date, 11 randomized clinical trials are underway with different agents as adjuvant systemic drug therapy to prevent the recurrence of HCC following curative resection according to *Clinicaltrial.gov*. Adjuvant systemic drugs may be the most promising of all adjuvant modalities in the near future since HCC may be a systemic disease rather than a local disease.

Keywords: Hepatocellular carcinoma, recurrence, adjuvant systemic drug

Hepatocellular carcinoma (HCC) is the fifth most common cancer leading to death worldwide and is estimated to cause half a million deaths annually. HCC is treated primarily by surgical curative resection. However, HCC frequently recurs postoperatively and has a negative impact on long-term survival. Most patients have intrahepatic recurrence, while a few have both intrahepatic and extrahepatic recurrence. The cumulative 5-year rate of intrahepatic recurrence is as high as 100% (*1*,*2*).

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Presumably, there are three causes of intrahepatic recurrence (*3*). Incomplete resection followed by residual tumor foci is responsible for early recurrence. Multicentric tumor may be responsible for late recurrence. Persistent viremiain dependently increases the recurrence of HCC in patients with underlying HBV and/or HCV infection, although the underlying mechanism remains unknown. Many attempts have been made to achieve better outcomes to prevent the recurrence of HCC following curative resection. In addition to surgical techniques, transcatheter arterial chemoembolization and immunotherapy have also been tried and tested, but their results were uncertain. Other approaches are systemic untargeted and molecularly targeted agents, though such agents are difficult to develop.

Unfortunately, many systemic untargeted agents are ineffective as adjuvant therapy to prevent the recurrence of HCC following curative resection according to available evidence. This is especially true for chemotherapy that was developed and tested mainly in 1990s and 2000s. For HCC with underlying conditions such as HBV or HCV infection, the potential effectiveness of interferon α as adjuvant therapy to prevent the recurrence of HCC has been proven in clinical trials and meta-analysis (*4*,*5*), although one multicenter clinical trial found it ineffective (*6*). Furthermore, a prospective clinical study and its updated analysis of the long-term follow-up data found that oral polyprenoic acid (acyclic retinoid) can prevent second primary HCC after surgical resection of original HCC since acyclic retinoid may delete malignant clones before such clones expand into detectable HCC (*7*,*8*) (Table 1). However, no other studies have reported polyprenoicacid (acyclic retinoid) to be effective.

According to currently available evidence, there is only one systemic molecular targeted agent, sorafenib (Table 1), that has proven effectiveness as adjuvant therapy for HCC to prevent early recurrence after hepatic resection (continuous sorafenib 400 mg *q.d.* for 4 months after hepatic resection). However, the study that yielded that finding was just a pilot study (*9*).

HCC is a genetically heterogeneous tumor, complicating its treatment with a single agent. Since

Table 1. Agents that are potentially effective as adjuvant systemic drugs according to current evidence

Items	Drug	Chemical formula
Untargeted agents	Interferon α	$C_{896}H_{1395}N_{245}O_{261}S_9$
	Acyclic retinoid	(2E,4E,6E,10E)-3,7,11,15-Tetramethylhexadeca-2,4,6,10,14-pentaenoic acid
Targeted agents	Sorafenib	4-[4-[[4-Chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-*N*-methyl-pyridine-2-carboxamide

Table 2. Ongoing clinical trials with adjuvant systemic drugs toprevent the recurrence of HCC according to *ClinicalTrials.gov*

Items	Drug	Trial phase	Current status	*ClinicalTrials.gov* identifier	Estimated primary completion date
Untargeted agents	Lamivudine or entecavir	IV	Unknown	NCT00768157	2009-09
	Adefovirdipivoxil and lamivudine	III	Ongoing, not recruiting	NCT00455091	2012-04
	Interferon-α-2b and ribavirin	IV	Ongoing, not recruiting	NCT00375661	2012-12
	Thymopentin	III	Unknown	NCT00460681	2012-02
	Ginsenoside Rg3 capsules	I-II	Recruiting	NCT01717066	2014-12
	Huaier granules	IV	Enrolling	NCT01770431	2014-10
Targeted agents	Sorafenib	III	Ongoing, not recruiting	NCT00692770	2014-05
	Gefitinib	II	Unknown	NCT00282100	2012-12
	PI-88	III	Recruiting	NCT01402908	2013-12
	Capecitabine	II-III	Unknown	NCT00561522	2012-07
	Tyroserleutide	III	Enrolling	NCT01489566	2013-03

sorafenib became the first agent to provide a significant improvement in overall survival and began serving as the standard treatment for patients with advanced HCC and Child-Pugh class A liver cirrhosis (*10*), several important signaling pathways of angiogenesis and proliferation have been identified in relation to hepatocarcinogenesis. These include Ras/Raf/MEK/ERK (MAPK), phosphoinositol-3 kinase (PI3k)/Akt/mTOR, hepatocyte growth factor (HGF)/c-mesenchymal epithelial transition factor (c-Met), insulin growth factor receptor, transforming growth factor-β, Wnt/β-catenin, Hedgehog and Notch (*11*). Several agents are being developed and tested in clinical trials. A phase III randomized, double-blind, placebo-controlled clinical trial (STORM) is underway to further evaluate sorafenib as adjuvant systemic drug therapy to prevent the recurrence of HCC following curative resection. This trial is active but not recruiting and is estimated to be completed by 2014-05.

Besides the STORM clinical trial, there are 10 other clinical trials with different agents as adjuvant systemic drug therapy to prevent the recurrence of HCC following curative resection (Table 2). Five agents can be categorized as systemic molecular targeted agents. One is heparanase inhibitor PI-88, which was tested in a phase III clinical trial that terminated. Another phase III clinical trial with heparanase inhibitor PI-88 is underway. Six agents can be categorized as systemic untargeted agents. Three of the six can be subcategorized as systemic antiviral agents, one can be subcategorized as a systemic immune agent, and the remaining two can be subcategorized as systemic herbal agents.

Since recurrence remains a key obstacle to a better prognosis for HCC following curative resection, a modality targeting recurrence would be crucial. To date, there are no globally accepted adjuvant systemic drugs with strong evidence of effectiveness, but adjuvant systemic drugs are being painstakingly developed and clinically tested. Adjuvant systemic drugs may be most promising of all modalities in the near future since HCC may be a systemic disease rather than a local disease.

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