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REVIEW ARTICLE

Clinical Development and Future Direction for the Treatment of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and about 600,000 patients suffer from HCC annually. The highest incidence is in Southeastern and Eastern Asia, with an incident rate of 18.3–35.5 per 100,000 population, and the lowest is in Central America with a rate of 2.1 per 100,000 population. HCC is one of the leading malignancies in Taiwan. Hepatitis B or C virus infections are the major factors for liver cancer in Taiwan. The survival time for patients with HCC without therapy after diagnosis averages 1–4 months. In this article, we review the risk factors, diagnostic criteria, staging systems, management and treatment of HCC. Treatments include liver transplantation, surgery, transcatheter arterial chemoembolization and transcatheter arterial embolization, percutaneous injection or radiofrequency ablation, chemotherapies, hormone therapy, internal radiation therapy, targeted therapy, a combination of chemotherapeutic agents and tyrosine kinase inhibitors, antiangiogenesis therapy, metabolic targets and Chinese herbal medicine. We propose three flow charts to guide surveillance, diagnosis, and treatment. Patients with high risk of HCC should be followed-up using the *HCC High Risk Group Surveillance Flow Chart 1*. If a mass is suspected, patients can be diagnosed using the *HCC Diagnosis Flow Chart 2*. On confirmation of HCC diagnosis, treatment should follow the *HCC Treatment Flow Chart 3*. Because the liver is the body's detoxification organ, its cells are already numerous with a high expression of the MDR gene. This makes chemotherapeutic drug treatment difficult. New molecular targeted therapy or new effective drugs are needed for difficult-to-treat HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and about 600,000 patients suffer from HCC annually. The highest incidence is in Southeastern and Eastern Asia, with a rate of 18.3–35.5 per 100,000 population, and the lowest is in central America, with a rate of 2.1 per 100,000 population. The rate of liver cancer in men is typically two to four times higher than in women, but is equal with women after menopause. Attributable risk estimates for the combined effects of hepatitis B and C virus infections account for well over 80% of liver cancer cases worldwide.[1,2] HCC is one of the leading malignancies in Taiwan, with 10,092 cases in 2006 and mortality of 7809 individuals in 2007 (Bureau of Health Promotion, Department of Health, Taiwan, available at http://www.bhp.doh.gov.tw). About 70% of cases fail to respond favorably to all available local therapies due largely to rapid decomposition with huge tumor burden. The major risk factor for

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Table 1 Child-Pugh classification

Measure	1 point	2 points	3 points
Total bilirubin (mg/dL)	<2	2–3	>3
Serum albumin (g/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (s) prolonged than that of control (INR value)	1–4	4–6 (>1.49)	>6 (>1.66)
Ascites	None	Slight	Moderate
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

INR = international normalized ratio.

HCC is liver cirrhosis due to hepatitis B or C virus infection in Taiwan. The mean survival time for patients with HCC without therapy is 1–4 months after diagnosis.[3]

2. Anatomical Distribution

The whole liver is subdivided into eight segments, based on understanding of the distribution of portal veins and hepatic veins, as described below:[4]

- Segment 1: caudate lobe;
- Segment 2: left lateral superior segment;
- Segment 3: inferior left lateral segment;
- Segment 4a: superior subsegment of the medial segment;
- Segment 4b: inferior subsegment of the medial segment;
- Segment 5: anterior inferior segment;
- Segment 6: posteroinferior segment;
- Segment 7: posterosuperior segment;
- Segment 8: anterior superior segment.

3. Risk Factors

Liver cirrhosis is the main precursor to HCC. Approximately 70–80% of patients with HCC in Asia and Africa and 21% of patients in the United States have HCC as a result of hepatitis B-related cirrhosis. In Asia, 10–20% of HCC patients have hepatitis C-related cirrhosis. Other rare risk factors of cirrhosis include genetic factors such as hemochromatosis, and congenital metabolic diseases such as glycogen storage disease type 1, alpha-1-antitrypsin deficiency, hereditary tyrosinemia and porphyria. Toxins, especially alcohol, aflatoxin B, and smoking are other risk factors for HCC, as are male sex and older age.[1,5]

4. Diagnostic Criteria

Typical vascular patterns of HCC, i.e., hypervascularization in arterial phase and wash-out of vascular stains in portal phase, can be demonstrated by dynamic imaging techniques [computed tomography (CT) or magnetic resonance imaging (MRI)]. Because the majority of HCC patients have underlying cirrhosis and histologic/cytologic examination may be associated with increased risk of bleeding, noninvasive diagnostic criteria have been established. For cirrhotic patients with focal lesions >2 cm, HCC can be diagnosed if: (1) two imaging techniques (CT and MRI) show typical vascular patterns; or (2) one imaging technique (CT or MRI) shows typical vascular patterns and there is an elevated α-fetoprotein (AFP) level (>200 ng/mL).[6]

Table 2 Okuda staging system

Positive features
- Tumor(s) involving >50% of the liver
- Ascites
- Albumin <3 g/L
- Bilirubin >3 mg/dL

Stage I: no positive features
Stage II: 1–2 positive features
Stage III: 3–4 positive features

5. Staging Systems

The Child-Pugh staging system scores observed findings on encephalopathy, ascites, albumin, prolonged prothrombin time and bilirubin. A total score of 5–6 points is defined as Class A, 7–9 points is Class B, and 10–15 points is Class C (Table 1).[7]

The Okuda staging System is divided into three stages, I, II and III, depending on the number of positive features out of a total of four: tumor size, ascites, serum albumin, and serum bilirubin (Table 2).[8]

The CLIP staging system scores the following items from 0 to 2: Child-Pugh class, tumor extent and morphology, serum AFP and portal vein thrombosis (Table 3).[9]

The AJCC (American Joint Commission of Cancer) 2002 staging system looks at whether the tumor is solitary or if there are multiple tumors, whether the tumor size is $\leq$5 cm or > 5 cm, whether there is vascular invasion, regional lymph node metastasis or distant metastasis (Table 4). The patient's liver function reserve is not considered.[10]

Table 3 CLIP staging system

Variable	Score
Child-Pugh class	
A	0
B	1
C	2
Tumor extent and morphology	
Uninodular and extension ≤ 50%	0
Multinodular and extension ≤ 50%	1
Massive or extension > 50%	2
α-fetoprotein (ng/dL)	
< 400	0
≥ 400	1
Portal vein thrombosis	
No	0
Yes	1

The BCLC (Barcelona Clinic Liver Cancer) staging system incorporates tumor characteristics (tumor size and number, vascular invasion, and extrahepatic spread) and patient characteristics (Child-Pugh liver function class and performance status) and assigns different treatment strategies to different stages (Table 5).[11]

6. Management of HCC

6.1. Liver transplantation

The different criteria for liver transplantation for HCC are shown in Table 6. According to the UNOS criteria, patients are eligible to undergo liver transplantation if they fall into these categories:

- Stage I, T1 tumor is ≤ 1.9 cm;
- Stage II, T2 single lesion measuring 2–5 cm or ≤ three tumors with the maximal diameter of each tumor < 3 cm.

Table 4 AJCC 2002 staging system

Stage	TNM	Description
Stage I	T1N0M0	Solitary tumor without vascular invasion
Stage II	T2N0M0	Solitary tumor with vascular invasion or multiple tumors none > 5 cm
Stage III		
IIIa	T3aN0M0	Multiple tumors, any > 5 cm (T3a)
IIIb	T3bN0M0	Tumor involving a major branch of the portal or hepatic vein(s) (T3b)
IIIc	T4N0M0	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Stage IV		
IVa	Any T, N1M0	Regional lymph node metastasis
IVb	Any T/N, M1	Distant metastasis

AJCC = American Joint Committee on Cancer; TNM = tumor node metastasis.

Table 5 BCLC staging system

BCLC stage	ECOG performance status	Tumor status		Liver function status
		Tumor stage	Okuda stage	
Stage A: early HCC				
A1	0	Single	I	No portal hypertension, normal bilirubin
A2	0	Single	I	Portal hypertension, normal bilirubin
A3	0	Single	I	Portal hypertension, abnormal bilirubin
A4	0	3 tumors < 3 cm	I–II	Child-Pugh A–B
Stage B: intermediate HCC	0	Large multinodular	I–II	Child-Pugh A–B
Stage C: advanced HCC	1–2	Vascular invasion or extrahepatic spread	I–II	Child-Pugh A–B
Stage D: end-stage HCC	3–4	Any		Child-Pugh C

BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma.

Table 6 Criteria of liver transplantation for hepatocellular carcinoma

UNOS criteria	Single tumor ≤ 5 cm, maximum of 3 total tumors with none > 3 cm
UCSF criteria	Single tumor ≤ 6.5 cm, maximum of 3 total tumors with none > 4.5 cm, and cumulative tumor size < 8 cm
"Up-to-seven" criteria	Seven as the sum of the size of the largest tumor (in cm) and the number of tumors

UNOS = United Network for Organ Sharing; UCSF = University of California, San Francisco.

Seventy percent of patients achieve a 5-year survival rate. In Taiwan, the waiting time is typically > 6 months, while the dropout rate has increased, and living donor liver transplantation has increased. Patients are often already receiving chemoembolization prior to transplantation.[12]

The UCSF criteria are: a single tumor ≤ 6.5 cm, or a maximum of three lesions with the largest one ≤ 4.5 cm, or cumulative size of all the tumors < 8 cm.[13]

The simple "Up-To-Seven" criteria are: seven as the sum of the size of the largest tumor (in cm) and the number of tumors.[14]

6.2. Partial hepatectomy

Indication for surgery should be determined by the size, number, and location of the tumors, the presence of vascular invasion, and the patient's liver function reserve. Liver function can be evaluated by the indocyanine green retention rate at 15 minutes (ICG R15). To be eligible for lobectomy, R15 should be < 10%. For 1/4 or removal of two segments, R15 should be < 15%. If R15 is < 25%, then only 1/8 segmentomy or removal of 1 segment should be considered. If R15 is < 35%, then only enucleation should be performed, and if R15 is ≥ 35%, then surgery is not recommended. From a large data series from Japan with 5800 patients, the postoperative 1-, 2-, 3-, 4- and 5-year survival rates were 85%, 60%, 52%, 48% and 36%, respectively.[15,16]

6.3. Transcatheter arterial chemoembolization and transcatheter arterial embolization

The rationale for using transcatheter arterial chemoembolization (TACE) or transcatheter arterial embolization (TAE) to treat HCC is based on the differences in blood supply between HCC and the normal liver. In a normal liver, 20–25% of the blood supply is from the hepatic artery, and 75–80% is from the portal vein. In contrast, in typical HCC, 90–100% of the blood supply is from the hepatic artery, and 0–10% is from the portal vein.

For patients who are not eligible for surgical intervention, TACE is the frontline treatment in most Asian countries if they have hypervascular tumor, patent main portal vein, serum albumin > 3 mg/dL, total bilirubin < 3 mg/dL and no evidence of extrahepatic metastasis. In TACE, chemotherapeutic agents such as cisplatin, mitomycin and adriamycin are commonly used. For embolization, Gelfoam particles and lipiodol are all commonly used.

The exclusion criteria for TACE/TAE are performance status ECOG (Eastern Cooperative Oncology Group) 3–4, Child-Pugh Class C or Okuda Stage III, infiltrative HCC, portal vein thrombosis (main or both first branches), presence of marked arteriovenous shunting, peripheral artery catheterization bleeding tendency, severe cardiopulmonary illness, and allergy to intravenous contrast medium. Presence of extrahepatic metastases is a relative contraindication of TACE. Some physicians use TACE to control the growth of intrahepatic tumors even in the presence of extrahepatic spread, but the actual clinical benefit is variable.[17,18]

The survival benefit of TACE was demonstrated by a meta-analysis of seven randomized controlled trials. The 2-year survival rate ranged from 19% to 63% in the TACE/TAE-treated groups and 11% to 50% in the control groups. The odds ratio was 0.53 (95% confidence interval, 0.32–0.89) favoring TACE treatment.[19]

6.4. Percutaneous injection or radiofrequency ablation

Percutaneous injection can be done by direct injection into the tumor of 95% ethanol, hypertonic saline, NaOH (2N) or acetic acid (50% glacial acid). In radiofrequency ablation, a 14-gauge needle is directed into the tumor by ultrasound or CT guidance and an alternating current, similar to microwave, is applied. This therapy is best for tumors < 5 cm. There is a complication rate of 2–17% with radiofrequency ablation; complications include bleeding, biliary fistula or stricture, abscess, arteriovenous fistula/aneurysm and needle track seeding. Four-year survival rates ranged from 60% to 80% in well-selected patient populations.[20,21]

6.5. Chemotherapy

Chemotherapy is usually given to patients with metastatic, persistent or recurrent disease. Single-agent treatment, such as doxorubicin, platinums, fluoropyrimidines, and gemcitabine, produce an objective response rate of ≤ 10% without proven survival benefit. Combination chemotherapy can improve the response rate to around 20%, but treatment-related toxicity, mainly myelosuppression, is also much higher. The limiting factors of chemotherapy for HCC patients are

Table 7 Summary of clinical trial experience for hepatocellular carcinoma at the National Health Research Institutes, Taiwan

Chemotherapy and/or biological modifier	
Phase I	Vit K3
Phase II	Vit K3 + 5FU/LV
Phase II	5FU
Phase II	5FU + IFN-α
Phase II	Paclitaxel
Phase II	EAPFL (doxorubicin, etoposide, cisplatin, 5FU, leucovorin)
Biological modifier	
Phase II	All-trans retinoic acid
Phase III	Adjuvant IFN-α
Radioisotope	
Phase II	Lipiodol I^{131}, Y^{90}, Re^{188}
Hormone	
Phase II	Megestrol: 160 mg, 800 mg
Phase II	Flutamide

No single drug or combination of drugs given systemically led to reproducible response rates > 25% or had any effect on survival beyond that of untreated control.

5FU = 5-fluorouracil; LV = leucovorin; IFN = interferon.

impaired liver function reserve, hypersplenism, and cytopenia, all resulting from the underlying cirrhosis.[22] Identification of new, effective chemotherapy drugs and other modalities for advanced HCC is urgently required. Below, we, at 191A Ward, a Collaborative Clinical Trial Ward of the National Health Research Institutes, which is supported by the Department of Health, Taiwan, briefly report our clinical trial experience for HCC (Table 7).[23]

6.5.1. Phase I study of vitamin K3 in HCC treatment

Menadione (vitamin K3) sodium bisulfite salt or tetrasodium salt of the diphosphoric acid-ester compound are converted in the body to menadione, and this is an FDA-approved indication for the treatment of hypoprothrombinemia. We found that it induces cell cycle arrest and apoptosis in nasopharyngeal carcinoma cells. In our Phase I clinical trial, we tested 50 mg/m^2 of menadione, and no specific toxicities were seen.

6.5.2. Phase II study of 5FU with and without interferon-α in advanced primary HCC

The focus of this study was on response rate while minimizing toxicity due to treatment and maximizing survival time. The regimen comprised 5FU 750 mg/m^2 continuous intravenous infusion from days 1 to 5, followed by 1 week of rest. Then, from the beginning of week 3 or day 15, 5FU 750 mg/m^2/week of intravenous bolus injection was given. Interferon-α (IFN-α) 9 μg was given thrice weekly intramuscularly or subcutaneously from day 1. Treatment duration was 12 weeks. If a favorable response was observed or stable disease status achieved, patients received treatment for another 12 weeks, up to a maximum of 6 months. Treatment was stopped at 6 months or earlier if there was disease progression. A total of 41 cases were enrolled: 21 in the 5FU plus IFN-α arm and 20 in the 5FU alone arm. Only one response was noted and the major adverse events included hematological toxicity and diarrhea.

6.5.3. Phase II study of paclitaxel in HCC treatment

Paclitaxel is one of the most active anticancer drugs introduced in the last two decades. It is active as salvage therapy in patients with various advanced cancers such as ovarian, breast, lung, and head and neck cancers. Twenty patients were studied; median age was 64 years (age range, 30–73 years). Four patients had liver dysfunction. The median number of courses of paclitaxel given was 2 (range, 1–7 courses). There was no complete or partial response seen. Thirty-six percent of patients had stable disease. The major treatment toxicities (grades 3–4) were mainly neutropenia (35%), thrombocytopenia (15%), infection (10%) and allergy (10%). Treatment-related death occurred in two patients.

6.5.4. Phase II study of EAPFL in HCC treatment

The schema of this protocol is: intravenous doxorubicin 30 mg/m^2 for 30 minutes on day 1; intravenous etoposide 40 mg/m^2/d for 30 minutes on days 1, 2 and 3; intravenous cisplatin 20 mg/m^2/d continuous infusion on days 1, 2 and 3; leucovorin 40 mg/m^2/d continuous infusion on days 1, 2 and 3; and intravenous 5FU 400 mg/m^2/d continuous infusion on days 1, 2 and 3. A total of 10 patients were enrolled. No significant anticancer effect of this protocol was observed. One patient had grade 4 thrombocytopenia, five patients had grade 4 leukopenia, two patients had grade 3 thrombocytopenia, and two patients experienced vomiting.

6.5.5. Phase II study of tretinoin in advanced HCC

The retinoid tretinoin, also known as all-trans-retinoic acid, is a semi-synthetic derivative of vitamin A. Its exact mode of action is unknown. It is a powerful differentiating agent and experimental evidence suggests that retinoid acid is responsible for limb-bud development and modulation of central nervous system development. A total of 19 patients were enrolled in this study. Tretinoin 45 mg/m^2 was taken orally for 1 week followed by 1 week of rest. The duration of observation ranged from 1 week to 1 year. No objective tumor responses were noted.

6.5.6. Phase III randomized trial comparing adjuvant IFN-α vs. conservative treatment in postoperative HCC

IFN-α is an active antiviral cytokine with antiproliferative action in many types of human cancers. It has been used successfully in the management of malignancies such as hairy cell leukemia, multiple myeloma, chronic myelogenous leukemia, low-grade non-Hodgkin's lymphoma, and renal cell carcinoma. In HCC patients who have had curative resections, approximately 40–60% had postoperative recurrence. More than 80–90% of them developed intrahepatic recurrence and only 10–20% had distant metastases. The 5-year disease-free survival rates were around 30%.[24,25] After screening more than 4000 HCC patients who had been operated on from 10 major teaching hospitals in Taiwan, we finally recruited 268 eligible patients. The majority of them adhered well to the study protocol, and only 18 of 133 patients in the IFN-α arm did not complete treatment because of withdrawal of consent or excessive toxicity. In addition, only two of the 268 patients were lost to follow-up after a median of 64.5 months of follow-up. The results indicated that adjuvant interferon did not significantly improve disease-free survival or overall survival for HCC patients who received curative resection.[26]

6.6. Hormone therapy

6.6.1. Phase II study of megestrol acetate in HCC

A total of 46 patients with advanced HCC were studied. Oral megestrol acetate 160 mg/day was given. Thirty-two patients were eligible for analysis and they were evaluated for tumor response, changes in appetite, weight, and feeling of wellbeing. There were no patients with complete or partial response. Twelve patients (38%) had stable disease, seven of whom had minor response with a median tumor size reduction of 18%. Twenty of the 32 (63%) patients had increased appetite and a feeling of wellbeing. The overall median survival of the 46 patients was 4 months (range, 1 week to 27 months). Glucocorticoid receptors were evaluated in the tumor tissue of 10 patients. Four of the five patients with positive glucocorticoid receptors had stable disease, and all five patients with negative glucocorticoid receptors had progressive disease ($p = 0.024$). Megestrol acetate did not result in any significant tumor response in patients with HCC, but it improved appetite, weight gain and the feeling of wellbeing with minimal side effects, some minimal response and stable disease. It is useful in the palliative management of HCC patients.

6.6.2. Phase II study of flutamide in HCC

Thirty-two patients with HCC were studied. Flutamide 750 mg/day was administered orally for 8 weeks. Ten patients died before the repeat tumor measurements could be performed. Twenty-two patients were evaluable for response and toxicities. Only 9 (41%) of the 22 had stable disease. Serum AFP was reduced in three patients. No toxicities were observed. Median survival was 10 weeks (range, 1–35 weeks). Flutamide did not appear to be effective for the treatment of advanced HCC, which indicates that HCC might not be an androgen responsive tumor.

6.7. Internal radiation therapy

We performed Phase II studies of lipiodol I^{131}, yttrium 90 (Y^{90}), and lipiodol Re^{188}. Lipiodol is a contrast medium consisting of an ethyl ester of the fatty acid of linseed oil, which remains in hepatomas much longer than in normal tissues when injected. Deposits of lipiodol may remain for as long as 1 year. Iodine is one of the major components of lipiodol (approximately 40%), and radioactive iodine (I^{131}) has been used effectively to clinically treat thyroid cancers. Using an isotopic exchange reaction to replace the iodine in lipiodol with I^{131}, this compound may then be used as a radiotherapeutic agent to specifically target hepatomas and deliver a high radiation dose to the tumor site. Of the nine patients evaluated, three had partial remission and three had stable disease; median survival was 10 months.[23]

Radioembolization with Y^{90} resin microspheres may be a new and promising palliative treatment option. The new modality of SIR-Spheres (SIRTEX Medical, Lake Forest, IL, USA) is approved for the treatment of patients with nonresectable malignant disease in Europe.[27]

In cooperation with the Department of Energy, we were able to obtain the new, effective, encouraging and potentially inexpensive radiopharmaceutical sulfur colloid isotope, lipiodol Re^{188}, for therapeutic use. Its maximum deep tissue penetration is 11 mm, but the average penetration is 3.8 mm with an energy of 2.13 MeV and a half-life of 17 hours. Preclinical trials in the treatment of malignant ascites from a melanoma cell line transplanted into SCID mice are ongoing. Bone marrow deposit of Re^{188} is much less than that of Y^{90}.[23]

6.8. Targeted therapy

In the era of molecular pathogenesis, many of the molecular pathways regulating cancer prognosis were discovered, leading to the development of novel targeted therapies. Promising molecular targets include vascular endothelial growth factor (VEGF) receptor, Raf/MEK/ERK signaling pathway, AKT/mTOR signaling pathway, epidermal growth factor receptor (EGFR), histone deacetylase (HDAC), Aurora kinases, proteasome, and platelet-derived growth factor receptor (PDGFR).[28]

Sorafenib is a recently developed multi-target drug. It inhibits the kinase activity of wild-type B-Raf and mutant Raf, VEGF receptors, PDGFR, c-kit, FLT3 and RET

(IC_{50} <100 nM). Sorafenib is antiproliferative and antiangiogenic. Hepatomas are mostly hypervascular tumors, with expression of proangiogenic factors [VEGF, fibroblast growth factor (FGF), matrix metalloproteinase (MMP)] in tumor and stromal cells. The first randomized, placebo-controlled trial of sorafenib for the treatment of advanced HCC (SHARP Trial) was done in Europe and the United States with the primary endpoint of overall survival. The second clinical trial was proposed as a bridging study to evaluate the overall efficacy and safety of sorafenib in the Asia-Pacific population.[29,30] The treatment—sorafenib 400 mg twice daily—was the same in both trials. Both trials were stopped early because interim analysis indicated significant survival benefit of sorafenib over placebo. The hazard ratios of overall survival and time to progression, respectively, were 0.69 and 0.58 in the SHARP trial and 0.68 and 0.57 in the Asia-Pacific trial. The subgroup analyses of the two trials showed that sorafenib treatment prolonged survival regardless of patients' vascular invasion or extrahepatic spread. Time to symptomatic progression was not significantly different between patients treated by sorafenib or placebo. The most common adverse events that occurred in about 20–40% of patients were diarrhea, fatigue, hand-foot skin reaction and rash and/or desquamation. These were the most common causes of treatment interruption or dose reduction.

Sorafenib has been approved for the treatment of advanced HCC by the European Medicines Agency and the US FDA. It is recommended by the US National Comprehensive Cancer Network as a treatment option for HCC patients who are inoperable or who do not present with cancer-related symptoms. However, its safety issues in patients with liver dysfunction need further clarification.[31]

The Phase III SHARP Trial screened 902 patients with HCC; 602 patients were randomized, 299 patients into the sorafenib arm (2 patients did not receive treatment) and 303 patients into the placebo arm (1 patient did not receive treatment). Accrual time was from March 2005 to April 2006. The protocol was stopped during the second interim analysis because of the results in overall survival. Median survival in the sorafenib arm was 46.3 weeks (10.7 months) versus 34.4 weeks (7.9 months) in the placebo arm. Median time to progression (independent review) in the sorafenib arm was 24 weeks (5.5 months) (95% CI, 18.0–30.0) versus 12.3 weeks (2.8 months) (95% CI, 11.7–17.1) in the placebo arm. The hazard ratio was 0.69 (95% CI, 0.55–0.87; $p < 0.001$) for overall survival and 0.58 (95% CI, 0.44–0.74; $p < 0.001$) for time to radiologic progression, both favoring sorafenib treatment.[29]

A randomized, double-blinded, placebo-controlled study of sorafenib in patients with advanced HCC was performed in the Asia-Pacific region, with complete accrual of 226 patients. The data management council suggested early termination on August 19, 2007 due to results in overall survival, time to progression and progression free survival, which were all significantly better in the treatment than in the placebo arm.[30] These two trials showed, for the first time in history, that a molecular targeted therapy prolonged survival in patients with advanced HCC. Sorafenib has also set a new standard for future clinical trials of advanced HCC treatment.

Clinical trials are being performed on the following molecular targeted therapies for HCC: sunitinib (marketed as Sutent, previously known as SU11248), TSU-68 (SU6688), vatalanib (PTK787/ZK222584), cediranib (AZD2171), bevacizumab (marketed as Avastin), gefitinib (marketed as Iressa, previously known as ZD1839), erlotinib (marketed as Tarceva, previously known as OSI-774), lapatinib (marketed as Tykerb, previously known as GW572016), BMS-599626, cetuximab (marketed as Erbitux, previously known as IMC-C225), AZD6244 (ARRY-142886), IMC-A12, everolimus (RAD-001), sirolimus (marketed as Rapamune), bortezomib (marketed as Velcade, previously known as PS-341), PI88, and belinostat (also known as PXD101).[28,32]

6.9. Combination of chemotherapeutic agents and tyrosine kinase inhibitors

A randomized Phase II trial of sorafenib plus doxorubicin versus doxorubicin alone reported superior median overall survival of 13.7 months versus 6.5 months and time to progression of 8.6 months versus 4.8 months in the combined therapy group compared to the doxorubicin alone group.[33] However, gemcitabine plus oxaliplatin compared with capecitabine plus oxaliplatin in advanced HCC had similar treatment efficacy in terms of tumor response and patient survival.[34–39]

A combination of antiangiogenic molecular targeted therapy with chemotherapy given in small doses on a frequent schedule in an uninterrupted manner for a prolonged period of time (metronomic chemotherapy) has also been tested in clinical trials.[40] Antiangiogenesis is a frequently cited mechanism of metronomic chemotherapy, and a synergistic antitumor effect may exist. These combination regimens include bevacizumab plus capecitabine,[41] sorafenib plus tegafur/uracil[42] and thalidomide plus tegafur/uracil,[43] and have shown disease-stabilizing effects in about half of advanced HCC patients.

6.10. Antiangiogenesis therapy

Angiogenesis plays a crucial role in the growth and progression of normal tissues and in a variety of tumors. Thus, antiangiogenesis was proposed as a potent anticancer treatment.[44,45]

Thalidomide, a glutamic acid derivative that was first described in 1953, was marketed as a sleeping pill and was very effective at ameliorating the morning sickness of pregnancy. However, it was withdrawn from the European market 30 years ago when it became

clear that it was a teratogen; its interference with blood vessels led to phocomelia.[46,47] Recent studies have shown that thalidomide can inhibit basic-FGF and VEGF-induced rabbit corneal neovascularization.[48,49] Most HCCs are hypervascular tumors, express pro-angiogenic factors (VEGF, FGF, MMP) in tumor and stromal cells, and produce circulating angiogenic factors. Several Phase II clinical trials have explored the efficacy of thalidomide as a treatment for advanced HCC.[50–53] Response was noted in approximately 5% of patients. About 10–30% of patients have stable disease for more than 2–4 months or longer after thalidomide therapy. Stabilized patients had decreased tumor vascularity, decreased blood perfusion and decreased AFP levels, some to normal range.[54,55] The most common drug-related toxicities, such as somnolence, constipation, dizziness and skin rash, were manageable. In a trial of low-dose thalidomide treatment of 63 HCC patients,[50] one complete and three partial responses were seen, with a response rate of 6.3% (95% CI, 0–12.5%). The duration of response in the four patients was 50+, 24.6, 11.6+ and 8.7+ weeks, respectively. All four responders had a dramatic decrease in AFP levels. Six of the 42 patients who had elevated AFP levels before treatment had a more than 50% decrease in their AFP levels after thalidomide therapy. A total of 10 patients had an objective response to thalidomide. Median overall survival of the 63 patients was 18.7 weeks (95% CI, 11.8–25.6 weeks), with a 1-year survival rate of 27.6%. Median overall survival of the 10 patients with an objective response to thalidomide was 62.4 weeks (95% CI, 31.2–93.6 weeks). All responders responded at a dose $\leq$300 mg/day. With regard to side effects, 16 patients had grade 2 toxicities, 6 patients had grade 3 toxicities, and no patients had grade 4 toxicities. Low-dose thalidomide appears to be safe and able to induce unequivocal tumor response in a minority of patients with advanced HCC.[50]

A Phase II trial of bevacizumab (10 mg/kg every 2 weeks) plus erlotinib (150 mg/day) for advanced HCC patients showed a response rate of 28% (14 partial responses out of 57 patients) and a median time to tumor progression of 7.9 months.[56] A second trial in Asia of a lower dose of bevacizumab (5 mg/kg every 2 weeks) plus erlotinib (150 mg/day) had a much lower response rate of 5.9% (3 partial responses out of 51 patients).[57] More studies in this category of treatment are needed to further clarify its benefits.

6.11. Metabolic targets

ADI-PEG 20 is composed of arginine deiminase (ADI), an arginine-degrading enzyme expressed from microbes in *Escherichia coli*, and polyethylene glycol (PEG), which delays immunogenicity and prolongs circulating half life. This drug can deplete ASS (argininosuccinate synthetase) levels and reduce the level of arginine in circulating blood. Cancer cells often have low or depleted levels of ASS and thus need external resources of arginine to sustain their daily needs. In a Phase I/II trial of ADI-PEG 20 in unresectable HCC, Delman et al showed that in 35 patients, 1 became resectable, 2 had stable disease, 4 did not complete the study, and 28 progressed with a mean duration before progression of 3.4 months.[58] A randomized Phase II study of ADI-PEG 20, 160 IU/m^2/week versus 320 IU/m^2/week, in advanced HCC was conducted in Taiwan. Seventy-one patients were enrolled. Both dosages of ADI-PEG 20 were well tolerated; most adverse events were hypersensitivity reaction of grades 1–2. No objective tumor response was seen. The median overall survival of all patients was 7.3 months. The relationship between circulating arginine levels after ADI-PEG 20 treatment and survival benefit will be explored (Yang TS et al, submitted for publication).

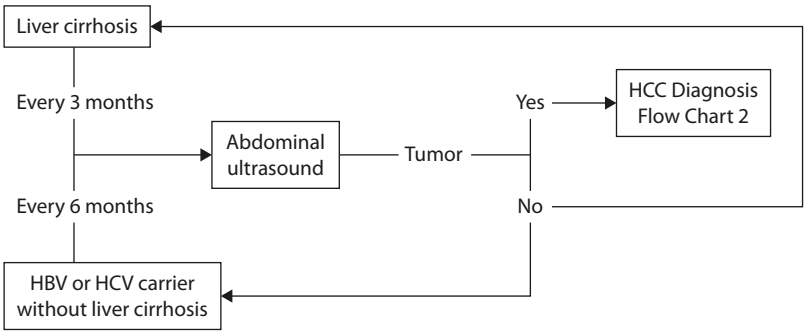
6.12. Chinese herbal medicine

Traditional Chinese medicine, such as botanical drugs, has recently been fast tracked through the FDA's newly established guidelines. Several clinical trials have been proposed.

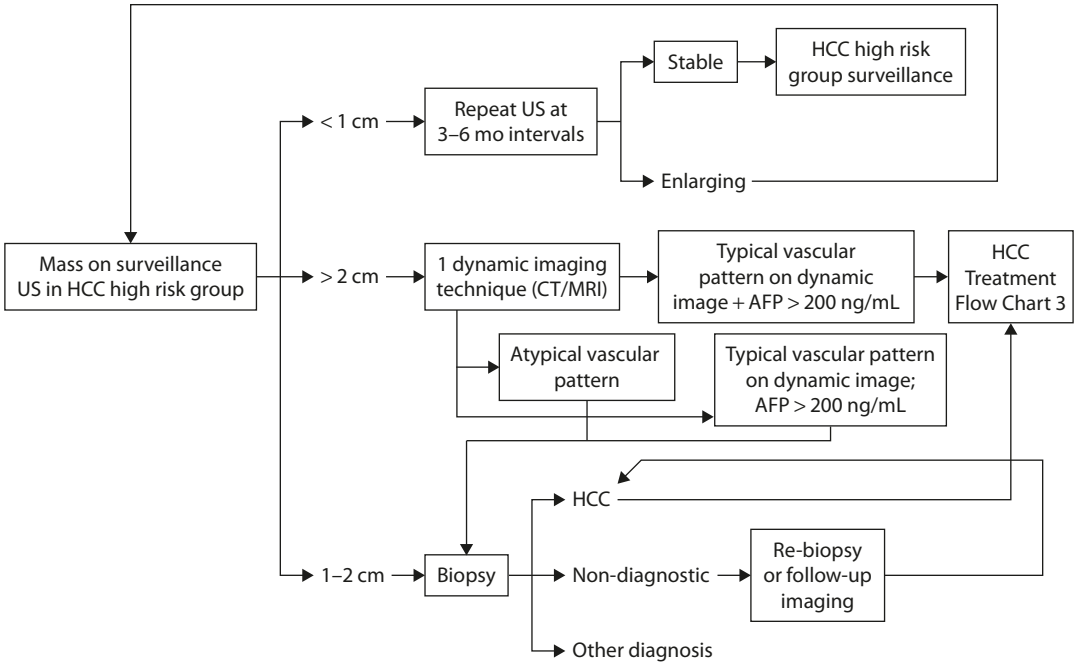
PHY906 has been in the Chinese pharmacopeia for over 1700 years and is mainly used for diarrhea, nausea, vomiting, abdominal cramps and fever. PHY906 contains four herbs: *Scutellaria baicalensis Georgi*, *Glycyrrhiza uralensis Fisch*, *Paeonia lactiflora Pall* and the fruit of *Ziziphus jujuba Mill*. In animal studies, a synergistic effect with chemotherapy drugs such as capecitabine and irinotecan (CPT-11) has been observed. A Phase I/II trial of PHY906 plus capecitabine for unresectable HCC was performed.[59] In this study, 18 patients were enrolled in Phase I and 24 patients in Phase II. Twenty-five (59.5%) patients were classified as Child-Pugh A and 17 (40.5%) as Child-Pugh B. All patients were eligible for safety evaluation. The results indicated that PHY906 600–800 mg twice daily, plus capecitabine 750 mg/m^2 twice daily, was generally well tolerated. More than 60% of patients had either stable disease or were better after two treatment cycles. Median overall survival was 9.2 months. A larger study of PHY906 plus capecitabine for patients with advanced HCC will be done at the National Health Research Institutes, Tainan site, and at Cheng Kung University Hospital.

7. Summary and Recommendation

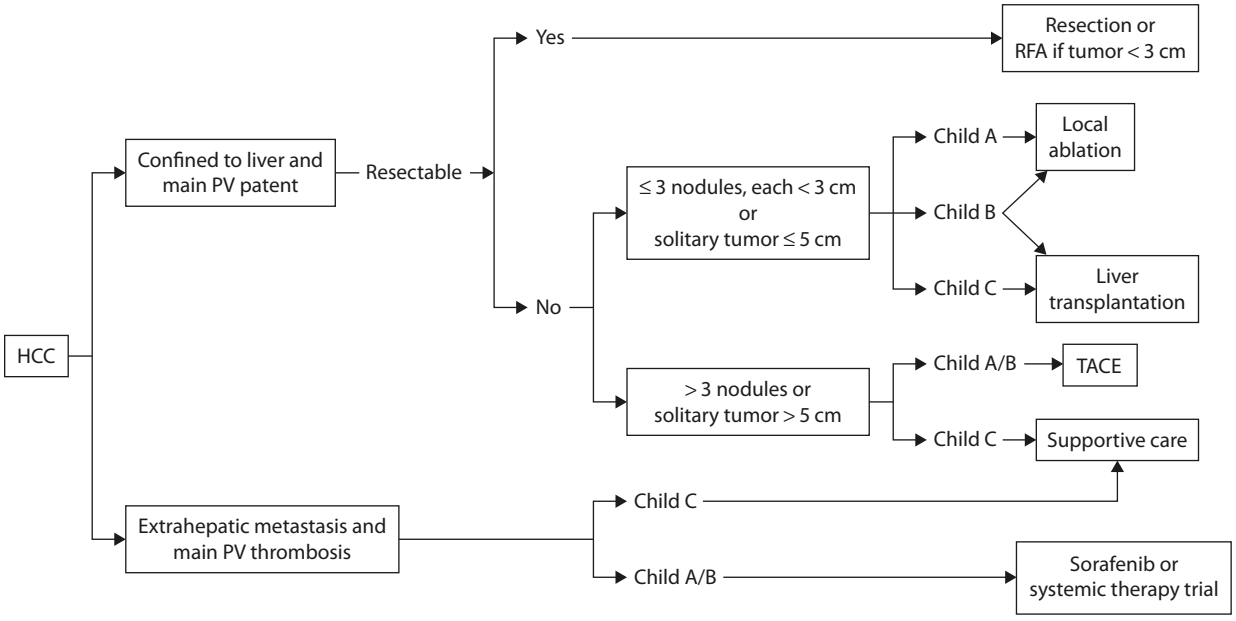
Hepatitis B or C virus infections are major factors leading to liver cancer. We propose three flow charts to guide surveillance, diagnosis, and treatment. For patients in the HCC high risk group, observation should follow the *HCC High Risk Group Surveillance Flow Chart 1*. Individuals are followed every 3 or 6 months with abdominal ultrasound. If a mass is suspected, patients are then diagnosed utilizing the *HCC Diagnosis Flow Chart 2*. A mass $<$1 cm will



Flow Chart 1 HCC High Risk Group Surveillance. HCC = hepatocellular carcinoma; HBV = hepatitis B virus; HCV = hepatitis C virus.



Flow Chart 2 HCC Diagnosis. US = ultrasound; HCC = hepatocellular carcinoma; CT = computed tomography; MRI = magnetic resonance imaging; AFP = α-fetoprotein.



Flow Chart 3 HCC Treatment. HCC = hepatocellular carcinoma; PV = portal vein; Child = Child-Pugh; RFA = radiofrequency ablation; TACE = transcatheter arterial chemoembolization.

continue to be monitored with ultrasound at 3–6-month intervals. A mass > 2 cm will require a dynamic imaging test (such as CT and MRI). For tumor size 1–2 cm, and if the dynamic imaging test shows a typical vascular pattern and AFP > 200 ng/mL, a confirmation biopsy is done for definite diagnosis. When the diagnosis of HCC is confirmed, then HCC treatment should follow *HCC Treatment Flow Chart 3*.

Many investigators are trying to find specific targets to develop HCC-specific drug therapy. As the liver is the body's detoxification organ, its cells already constitutionally have a high level of MDR gene expression, which makes chemotherapeutic drug treatment difficult. New molecular targeted therapy or new effective drugs are needed for the treatment of this resilient HCC.

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