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REVIEW ARTICLE

Recent Advances in the Treatment of Hepatocellular Carcinoma

RTP Poon

Department of Hepatobiliary and Pancreatic Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

ABSTRACT

Multiple factors may influence the selection of treatments for patients with hepatocellular carcinoma. Surgical resection continues to be the mainstay of treatment for patients with well-preserved liver function. Appropriately selected candidates can have a five-year postoperative survival rate of up to 70%, but hepatic resections are also associated with a high recurrence rate. Patients with small hepatocellular carcinoma tumours can be treated with radiofrequency ablation. However, this procedure is also associated with high recurrence rates. Microwave ablation can induce large ablation volumes and yield good local tumour control, especially for small tumours. High-intensity focused ultrasound can be safely used to ablate tumours adjacent to major vessels or hepatic ducts. Long-term survival after thermal ablation is comparable to that of surgery for tumours of 3 cm or smaller. Liver transplantation is considered to be curative of both the tumour and the underlying cirrhosis. Transplantation is associated with favourable long-term survival and low recurrence rates. However, graft availability, costs, and lack of local expertise may limit the availability of this procedure for many patients with hepatocellular carcinoma. For patients with well-preserved liver function and multinodular tumours without vascular invasion, transarterial chemoembolisation can be a suitable treatment. Transarterial chemoembolisation with doxorubicin-eluting beads is a newly developed locoregional treatment for unresectable hepatocellular carcinoma, and may be safer and more effective than conventional transarterial chemoembolisation. Yttrium-90 radioembolisation is a relatively new technique that implements transarterial administration of minimally embolic microspheres to deliver selective internal radiation to the tumour. So far, no prospective study has compared selective arterial radioembolisation with yttrium-90 microspheres with transarterial chemoembolisation, however, the latter has shown promise, particularly for hepatocellular carcinoma with portal vein invasion. Sorafenib has been approved for treatment of advanced hepatocellular carcinoma, with a gain in median survival of about three months. Other molecular targeted therapies for hepatocellular carcinoma are being evaluated in clinical trials. This paper provides an update on current and emerging treatment options for patients with hepatocellular carcinoma.

Key Words: *Carcinoma, hepatocellular; Chemoembolization, therapeutic; Molecular targeted therapy*

中文摘要

治療肝癌的最新發展

潘冬平

多項因素會影響肝癌患者選擇治療的方法。手術切除仍然是患者保存良好肝功能的主要療法，合適的病人術後五年的存活率可達至70%，但肝切除的復發率屬於偏高。如肝癌患者的腫瘤屬小型，可選擇射頻燒灼術，但此方法的復發率同樣偏高。微波燒灼術有較大燒灼量，尤其對於小型腫瘤，可

Correspondence: *Prof Ronnie TP Poon, Department of Hepatobiliary and Pancreatic Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong.*
Tel: (852) 2255 5907 ; Fax: (852) 2817 5475 ; Email: poontp@hku.hk

產生較佳的局部療效。高強聚焦超音波對於位置較接近大型血管或肝動脈的腫瘤屬於較為安全的方法。熱能燒灼術的遠期存活率可媲美腫瘤小於三厘米的切割手術。肝臟移植被認為是同一時間醫治腫瘤及相關肝硬化的方法。肝臟移植有良好的遠期存活率及低復發率，可惜的是，對於眾多的肝癌患者來說，活肝數量、治療成本、及本地醫療技術都限制肝臟移植的發展。對有良好肝功能而有多結節但無血管侵犯腫瘤的患者，肝動脈栓塞化療可能較為適合。以doxorubicin緩釋微球作肝動脈栓塞化療是治療不能手術切除肝癌的一種新研發的局部治療方法，比利用傳統肝動脈栓塞化療更安全、更有效。釔90放射性栓塞治療是一種相對較新的技術，經肝動脈中的微創栓塞微球以傳送選擇性的體內放射至腫瘤。直至目前為止，尚未有前瞻性研究比較釔90放射性栓塞治療與肝動脈栓塞化療，可是，肝動脈栓塞化療尤其對已侵襲門靜脈的肝癌較有保證。Sorafenib已獲准治療晚期肝癌的藥物，可延長病人的存活率中位數約三個月。目前正評估臨床試驗中其他分子標靶治療肝癌的成效。本文為肝癌患者提供了一個現時和新興的治療方案。

INTRODUCTION

Liver cancer is the fifth most common cancer in men and the seventh in women. Almost 85% of liver cancer cases occur in developing countries, with more than half of the estimated 750,000 new liver cancer cases in 2008 being diagnosed in China.[1] Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. The incidence worldwide varies according to the prevalence of hepatitis B and C infections. Areas such as Asia and sub-Saharan Africa with high rates of hepatitis B infection have incidences as high as 120 cases per 100,000 population.[2]

There were an estimated 694,000 deaths from liver cancer worldwide in 2008. The geographical distribution of mortality rates is similar to that observed for incidence.[1] HCC is the third most common cause of cancer deaths worldwide.[3] Most cases of HCC are secondary to either a viral hepatitis infection or cirrhosis, which complicates patient management and the search for safe and effective therapies. In Hong Kong, liver cancer is the third leading cause of cancer deaths.[4] Largely asymptomatic in the early stages, more than 70% of patients are diagnosed only in the advanced stages of the disease.[3] Typically diagnosed late in its course, the median survival following HCC diagnosis is approximately 6 to 20 months.[5]

CURRENT TREATMENTS FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

The optimal management of HCC depends on a variety of factors, including the size, number, and distribution of tumours, the relationship of the tumour to the hepatic vasculature, the status of distant metastases, the severity of underlying liver disease (i.e. Child-Pugh score), and the functional status of the patient, as well as on local expertise.

Several classification systems are available for HCC. The Barcelona Clinic Liver Cancer (BCLC) classification and treatment schedule (Figure 1[6]) is widely followed. However, the BCLC is considered a conservative treatment approach in Asia. The Asian Pacific Association for the Study of the Liver convened an international working party on the management of HCC in 2008 to develop consensus recommendations. The working party recommended that the treatment choice for a solid tumour should be decided taking into account the probability of cure and invasiveness of the treatments. As such, background hepatic function that can significantly affect overall survival (OS) should influence treatment options for HCC. In addition, the evidence suggests that the probability of local cure is not a good surrogate for survival in HCC because intrahepatic recurrence occurs frequently, even after curative resection. Therefore, a treatment algorithm that includes both tumour- and hepatic reserve–related factors was proposed for the management of HCC in the Asia-Pacific region (Figure 2).[7] This treatment guideline offers more aggressive surgery for HCC, including for patients with multiple tumours or intrahepatic portal vein branch invasion who are considered to be contraindicated for surgery in the BCLC classification. HCC treatments could be considered either curative or palliative.

CURATIVE HEPATOCELLULAR CARCINOMA TREATMENTS

Surgical Resection

Surgical resection is the mainstay of treatment in non-

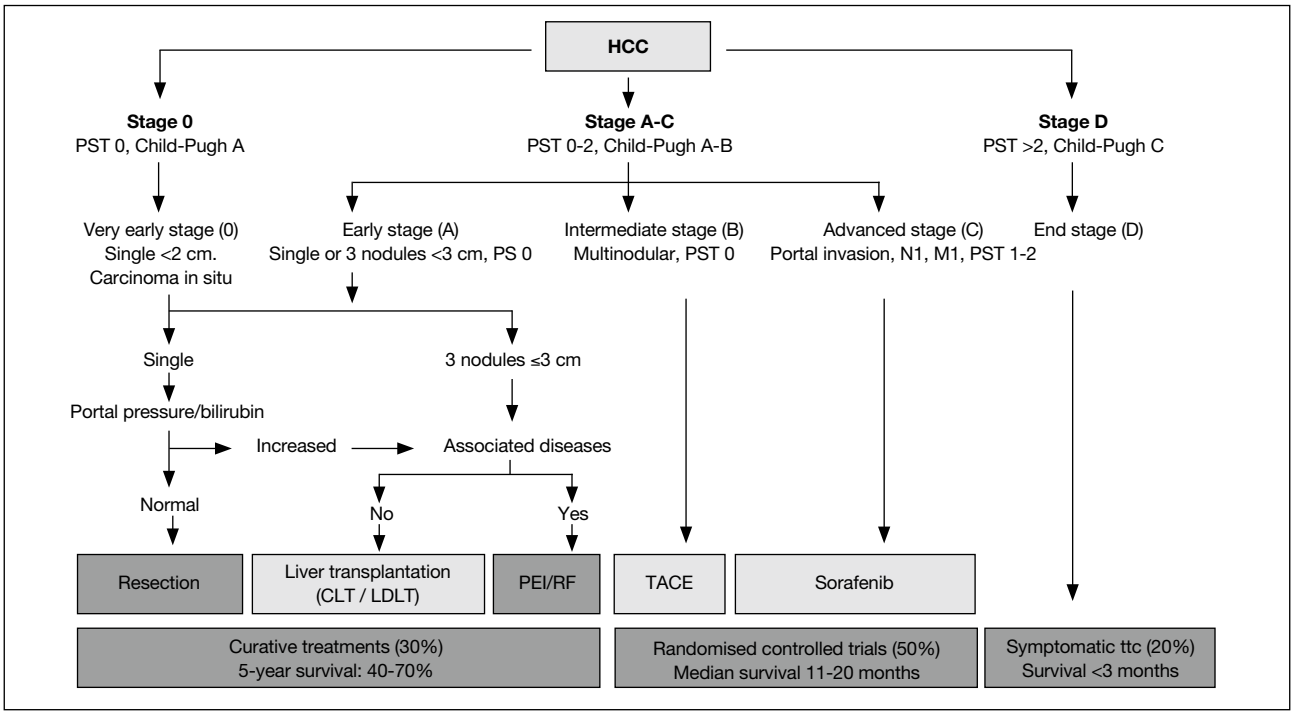

Figure 1. Barcelona Clinic Liver Cancer staging classification and treatment schedule.[6]
Patients with very early HCC (stage 0) are optimal candidates for resection. Patients with early HCC (stage A) are candidates for radical therapy (resection, liver transplantation, or local ablation via percutaneous ethanol injection or radiofrequency ablation). Patients with intermediate HCC (stage B) benefit from transarterial chemoembolisation. Patients with advanced HCC, defined as presence of macroscopic vascular invasion, extrahepatic spread, or cancer-related symptoms (Eastern Cooperative Oncology Group performance status 1 or 2; stage C) benefit from sorafenib. Patients with end-stage disease (stage D) should receive symptomatic treatment. Treatment strategy will change from one stage to another at treatment failure or contraindications for the procedures.
Abbreviations: CLT = cadaveric liver transplant; HCC = hepatocellular carcinoma; LDLT = live donor liver transplant; PEI = percutaneous ethanol injection; PST = performance status; RF = radiofrequency; TACE = transarterial chemoembolisation.

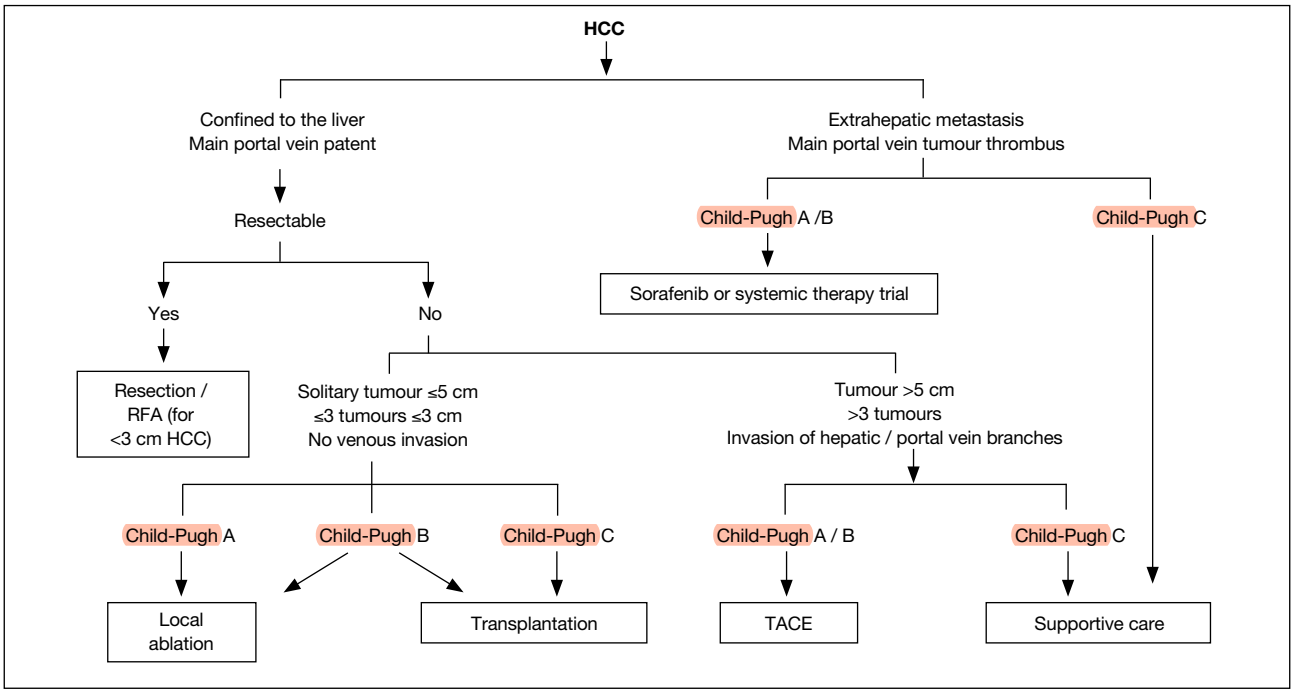

Figure 2. Asian Pacific Association for the Study of the Liver consensus on the treatment of hepatocellular carcinoma.[7]
Abbreviations: HCC = hepatocellular carcinoma; RFA = radiofrequency ablation; TACE = transarterial chemoembolisation.

cirrhotic, as well as cirrhotic, patients with HCC with well-preserved liver function (Child-Pugh class A).[8] The safety of surgical resection is well-established, and the mortality rate after hepatic resection in experienced centres is <5%.[9]

A study was conducted in Hong Kong to investigate whether survival after resection has improved by analysis of a prospective cohort of patients over a 10-year period (1989-1999).[10] The OS and disease-free survival (DFS) results were significantly better for those treated after 1994 than for those treated prior to 1994. There were also significantly lower frequencies of histological margin involvement, less intraoperative blood loss, and a lower transfusion rate in those who were more recently treated. Significant improvements in OS and DFS were noted after HCC resection as a result of advances in the diagnosis and surgical management of HCC. Early diagnosis of HCC through improved imaging modalities, increased detection of subclinical HCC by screening of high-risk patients, and a reduced perioperative transfusion rate were identified as the major contributory factors for the improved outcomes.

In another Hong Kong study conducted to assess the trends in perioperative outcomes of hepatectomy, factors associated with morbidity and mortality were analysed. The study found that perioperative blood transfusion increases risk of tumour recurrence and adversely affects long-term survival.[11]

Appropriately selected candidates for liver resection have five-year postoperative survival rates of 40 to 70%.[8] At the Queen Mary Hospital in Hong Kong, the three- and five-year survival rates of patients who underwent hepatic resection for HCC were 62% and 50%, respectively.[12] Nevertheless, long-term outcomes after surgical resection are curtailed by the high recurrence rate of about 70%.[13,14]

Local Ablation

Local ablative therapies have evolved over the years. First introduced in the 1990s as an alternative therapeutic modality to percutaneous ethanol injection therapy,[15] radiofrequency ablation (RFA) can be performed safely using percutaneous, laparoscopic, or open surgical techniques.[16] Since then, RFA has been widely used to treat unresectable malignant liver tumours. RFA has the merits of effective localised tumour ablation and preservation of maximal normal liver parenchyma.[17]

RFA is a localised thermal treatment technique designed to induce tumour destruction by heating the tumour tissue to temperatures that exceed 60°C.[18] Percutaneous RFA under local anaesthesia is the least invasive approach, although intraoperative RFA under general anaesthesia can also be performed in tumours located in a difficult position for percutaneous ablation or large tumours that require multiple overlapping ablation.[16]

A prospective randomised controlled trial of 180 patients showed that RFA is as effective as surgical resection in the treatment of solitary and small HCC tumours. The four-year OS and DFS were 64% and 52%, respectively.[19] In a Japanese study of 664 patients who received 1000 RFA treatments to 2140 nodules, the safety and efficacy of RFA for HCC were investigated. This study recorded no treatment-related deaths. Cumulative five-year survival rates for patients who received RFA as the primary treatment for HCC was 54%.[15]

Like surgical resection, local ablation of HCC is also associated with high recurrence rates. In one study, 56 patients with HCC tumours who received a single session, single application of percutaneous RFA and who achieved optimal tumour ablation had an overall cumulative local recurrence of 26% within 18 months.[20]

Although the results of most clinical studies of RFA seem favourable, the associated risks and tumour recurrence should not be underestimated. Careful patient selection, meticulous RFA techniques, and prompt treatment of residual and recurrent tumours are necessary to ensure optimal outcomes after RFA.[17] At some centres, patients can be offered a combination of resection and ablation as a result of multidisciplinary collaboration between surgeons and radiologists.

Other novel modalities of ablative therapy include the use of new microwave systems, ultrasound- or magnetic resonance imaging–guided high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE).

Microwave ablation uses heat generated from microwave energy applied directly to the tumour to destroy cancer cells. The new generation of microwave systems allows faster ablation of a large volume-diameter, which is particularly suited for operative ablation of large tumours. There is also minimal heat-sink effect in tumours close to major blood vessels.[21] A

review has shown that microwave ablation can induce large ablation volumes and yield good local tumour control, especially for small HCCs.[22] Large tumours can also be completely ablated by using a more effective antenna or simultaneous application of multiple antennae. Long-term survival comparable to that of surgery was obtained for tumours measuring ≤4 cm.

HIFU is a non-invasive, extracorporeal therapy that can be used on tumours that are difficult to treat with other techniques.[23] Short- and long-term follow-up shows that HIFU can be safely used to ablate the tumours adjacent to major vessels.[24] A Chinese study was conducted to determine the safety, efficacy, and feasibility of extracorporeal HIFU in the treatment of patients with HCC.[23] Follow-up imaging showed an absence of tumour vascular supply and shrinkage of treated lesions. The OS rates at 6, 12, and 18 months were 86.1%, 61.5%, and 35.3%, respectively.

IRE is a novel technology that uses a series of microsecond high-voltage direct current (up to 3 kV) to create multiple holes in the cell membrane to induce instant death in cancer cells. This is a non-thermal ablation technology that can be safely used near vital nerves, and vascular and ductal structures. There is virtually no heat-sink effect as no heat is involved in this treatment. A single-centre prospective non-randomised cohort study performed to investigate the safety of IRE for tumour ablation found the procedure to be safe for human clinical use provided electrocardiogram-synchronised delivery is used.[25]

Kingham et al[26] evaluated the safety and short-term outcomes of IRE to ablate perivascular malignant liver tumours. Their retrospective review of patients treated with IRE reported that overall morbidity was 3%. There were no treatment-associated mortalities. At median follow-up of 6 months, there was one tumour with persistent disease (1.9%) and three tumours recurred locally (5.7%). The authors concluded that this early analysis of IRE treatment demonstrated safety for treating liver malignancies.[26]

Liver Transplantation

Liver transplantation is considered to be curative of both the tumour as well as the underlying cirrhosis in well-selected patients. In optimal candidates, studies have shown that it is possible to achieve a 70% five-year survival rate with a recurrence rate of below 15%.[14,27-29] Sadly, there are limited grafts available due to the shortage of donors, resulting in a steadily increasing waiting period during which the outcomes of transplantation markedly deteriorate. Furthermore, transplantation and multidisciplinary expertise may not be available, particularly in those developing areas with the highest HCC incidence.[9] These factors, coupled with potential costs, may well limit the availability of liver transplantation for HCC patients.

PALLIATIVE HEPATOCELLULAR CARCINOMA TREATMENTS

Transarterial Chemoembolisation

Transarterial chemoembolisation (TACE), used to delay the progression of inoperable HCC, is a minimally invasive procedure to restrict a tumour's blood supply and induce cancer killing by delivering a high concentration of cytotoxic drugs directly to the tumour. TACE involves an arteriogram following percutaneous access to the hepatic artery to identify the tumour-supplying vasculature. Focused administration of chemotherapy directly to the tumour can reduce systemic side-effects.

A study performed to evaluate treatment results and prognostic factors of TACE treatment in inoperable HCC patients showed that TACE was associated with an overall treatment morbidity rate of 23% and mortality rate of 4.3%.[30] The overall five-year survival rate was reported to be 17%. The ideal candidates for TACE are patients with well-preserved liver function (Child-Pugh class A) and multinodular tumours without vascular invasion. In these patients, the benefits derived by achieving objective responses (30-50% of patients) are not offset by deterioration of the liver function.[31]

Chemoembolisation with doxorubicin drug-eluting beads (DEB) is a novel locoregional treatment modality for unresectable HCC. Initial animal studies and clinical trials suggest that treatment with DEB may provide safer and more effective short-term outcomes than conventional TACE.[32] With the soft deformable doxorubicin microspheres, blood flow to the tumour is reduced. This enhances the local anti-tumour effect while reducing systemic exposure.

PRECISION V is the first phase 2 trial comparing the efficacy and safety of DEB with conventional TACE.[33] Patients receiving DEB had higher rates of complete response, objective response, and disease control than the conventional TACE group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively). However, the

hypothesis of superiority was not met (one-sided p = 0.11). DEB was associated with improved tolerability, with a significant reduction in serious liver toxicity (p < 0.001) and a significantly lower rate of doxorubicin-related side-effects (p = 0.0001).

Prior to the aforementioned European phase 2 comparative study, a local phase 1/2 study (n = 35) had been conducted to assess the safety and efficacy of TACE using DEB for HCC.[34] The phase 1 trial was a dose-escalating study. In the phase I study, no dose-limiting toxicity was observed for up to 150 mg doxorubicin. The doxorubicin 150 mg dose was used for the phase 2 study. The treatment-related complication rate was 11.4% and there was no treatment-related death. In the phase 2 study, partial and complete response rates were 50% and 0%, respectively, by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria at computed tomography scan one month after the second TACE. By modified RECIST criteria, taking into account the extent of tumour necrosis, 63.3% of patients had a partial response and 6.7% had a complete response.

Transarterial Yttrium-90 Radioembolisation

Yttrium-90 (Y-90) radioembolisation is a relatively new technique that uses transarterial administration of minimally embolic microspheres loaded with Y-90, a β-emitting isotope, to deliver selective internal radiation to the tumour. So far, selective arterial radioembolisation with Y-90 microspheres has shown promise for regional management of HCC.[35]

A small study published in 2010 has shown this procedure to be well-tolerated and associated with a high rate of local tumour control in patients with unresectable HCC.[35] In another study, the anti-tumour efficacy and safety of Y-90 microspheres in HCC were assessed. Among 21 patients, a reduction in size of the target lesions was observed in all but one patient. When considering only target lesions, the disease control and response rates were 100% and 23.8%, respectively. However, 43% of patients progressed in the form of new lesions appearing in the liver in a median time of 3 months after radioembolisation.[36]

Sorafenib

To date, the oral multikinase inhibitor sorafenib, which exerts both antiangiogenic and antiproliferative effects, is the only approved oral systemic therapy for the treatment of advanced HCC. Preclinical studies show that Raf-1 kinase signalling and prolific tumour angiogenesis together play an important role in the evolution of HCC, lending a molecular rationale for the use of sorafenib in this malignancy.[37,38]

In the phase 1 setting, sorafenib demonstrated an acceptable safety profile, as well as the observation of a partial response in a patient with HCC.[39] The phase 2 trial of sorafenib in advanced HCC demonstrated minimal toxicity, but also little in the way of conventional RECIST responses.[40] Survival parameters were comparable to those of the best published combinations of systemic chemotherapy in advanced HCC.[40-42]

In the phase 3 setting, the SHARP (Sorafenib HCC Assessment Randomised Protocol) trial was a multicentre double-blind placebo-controlled study that randomly assigned 602 patients with advanced HCC who had not received previous systemic treatments to receive either sorafenib 400 mg twice daily or placebo.[43] Median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group (p < 0.001). There was no significant difference between the two groups in the median time to progression (TTP; 4.1 vs. 4.9 months, respectively; p = 0.77). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group (p < 0.001). Seven (2%) patients in the sorafenib group and 2 patients (1%) in the placebo group had a partial response; no patients had a complete response. Disease-control rate (a composite of complete response, partial response, and stable disease) was significantly higher in the sorafenib group (43% vs. 32%; p = 0.002). Diarrhoea, weight loss, hand-foot skin reaction, and hypophosphataemia were more frequent in the sorafenib group. In patients with advanced HCC, median survival and time to radiologic progression were found to be about three months longer for patients treated with sorafenib than for those given placebo.

A phase 3 multinational randomised double-blind placebo-controlled trial was conducted in the Asian setting to assess the efficacy and safety of sorafenib in patients from the Asia-Pacific region with advanced (unresectable or metastatic) HCC.[44] Patients with HCC (n = 271; 21 centres across Asia), who had not received previous systemic therapy and had Child-Pugh class A cirrhosis, were randomly assigned (on a 2:1 ratio) to receive either oral sorafenib 400 mg or placebo twice daily in 6-week cycles, with efficacy measured at the end of each 6-week period. Median OS was 6.5 months

in patients treated with sorafenib compared with 4.2 months in those who received placebo (p = 0.014). Median TTP was 2.8 months in the sorafenib group compared with 1.4 months in the placebo group (p = 0.0005). The most frequently reported grade 3/4 drug-related adverse events in patients treated with sorafenib were hand-foot skin reaction (10.7%), diarrhoea (6.0%), and fatigue (3.4%). These adverse events rarely led to treatment discontinuation. Together with data from the SHARP trial, these studies place sorafenib as an appropriate option for the treatment of advanced HCC.

In patients with Child-Pugh class B cirrhosis, patients with advanced HCC who were treated with sorafenib at Queen Mary Hospital, Hong Kong, were analysed retrospectively to explore the efficacy, tolerability, and survival benefits of using sorafenib in this patient population.[45] Clinical benefit rates for Child-Pugh B score 7 and Child-Pugh B score 8-9 (32% vs. 21%, respectively; p = 0.23) and PFS (median 3.2 months vs. 3.2 months; p = 0.26) were similar. Nonetheless, Child-Pugh B patients experienced more anaemia (p = 0.01), gastrointestinal bleeding (p = 0.02), and hepatic encephalopathy (p = 0.02). Currently, the phase 3 STORM (Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma) trial (NCT00692770) is being conducted to investigate sorafenib as adjuvant treatment in the prevention of recurrence after resection or ablation of HCC.

OTHER EMERGING TREATMENT MODALITIES FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

Heparanase Inhibitor Phosphomannopentaose Sulphate

Heparanase is a matrix-degrading enzyme that cleaves heparan sulphate (HS) side chains from the core proteoglycans. A sulphated oligosaccharide mimetic of HS, phosphomannopentaose sulphate (PI-88), was used to simultaneously inhibit both heparanase activity and HS effector functions. PI-88 had significant effects at distinct stages of tumour genesis, producing reduction in the number of early progenitor lesions and impairment of tumour growth at the later stages. These responses were associated with decreased cell proliferation, increased apoptosis, impaired angiogenesis, and substantial reduction in the number of invasive carcinomas.[46] Furthermore, heparanase expression correlated with metastasis and recurrence of HCC after resection.[47]

A phase 2 multicentre randomised trial investigated the safety, optimal dose, and preliminary efficacy of PI-88 as adjuvant therapy to reduce postoperative recurrence of HCC.[48] At the dose of 160 mg/day, PI-88 was shown to reduce recurrence compared with placebo when used as an adjunctive therapy in this group of patients. A phase 3 randomised trial of PI-88 involving 600 patients is ongoing in the Asia-Pacific region.

Systemic Therapy in Combination with Transarterial Chemoembolisation

Studies investigating combination therapy with sorafenib and TACE in intermediate-stage HCC include a Japanese/Korean study,[49] the SPACE (Sorafenib or Placebo in Combination with TACE for Intermediate-stage Hepatocellular Carcinoma) study,[50] ECOG (Eastern Cooperative Oncology Group)–E1208 (NCT01004978), and the TACE-2 study (NCT01324076). So far, only the Japanese/Korean study has been published. However, this study found that sorafenib did not significantly prolong TTP in patients who responded to TACE. The authors postulate that this may have been due to delays in starting sorafenib after TACE and / or low daily sorafenib doses.[49]

The SPACE study has also been completed.[50] This randomised double-blind trial of continuous sorafenib 400 mg twice daily or placebo given with TACE with DEB repeated at 3, 7, and 13 months, and every 6 months thereafter involved 307 patients with intermediate-stage HCC. Median treatment duration for sorafenib and placebo was 4.8 and 6.3 months, respectively. The study met its primary endpoint of improving TTP when sorafenib was added to a regimen of TACE with DEB compared with TACE with DEB alone (p = 0.072; significant at predefined α of 0.15).

The ORIENTAL (Orantinib In Combination With Transcatheter Arterial Chemoembolization In Patients With Unresectable Hepatocellular Carcinoma) study (NCT01465464) investigates the efficacy of the multikinase inhibitor orantinib plus TACE in HCC patients. The phase 2 TRACER (Safety and Efficacy of RAD001 + TACE in Localised Unresectable HCC) study (NCT01379521) involving patients from Hong Kong, Korea, Taiwan, and Thailand will evaluate the role of everolimus in combination with TACE using DEB in patients with localised unresectable HCC. Patient recruitment for this study has commenced.

Novel Molecular Targeted Drugs

Several novel molecular targeted therapies have also

been studied for the treatment of advanced HCC. For example, ongoing phase 3 trials for first-line therapy of advanced HCC include that for linifanib (ABT869; NCT01009593), which compares the efficacy of linifanib against sorafenib. The BRISK-FL (Brivanib Versus Sorafenib as First-line Treatment in Patients With Advanced HCC) trial (NCT00858871) investigates the efficacy of brivanib versus sorafenib in a randomised phase 3 setting; the sponsoring company has announced that the results are negative, although the full study has not yet been published.

Everolimus (EVOLVE-1; NCT01035229) and ramucirumab (REACH; NCT01140347) are being investigated in phase 3 trials for second-line therapy of advanced HCC. The SECOX (Sorafenib with Capecitabine and Oxaliplatin) study was a phase 2a trial of sorafenib with capecitabine and oxaliplatin in 51 patients with locally advanced or metastatic HCC.[51] In this single-arm multicentre study, the SECOX regimen demonstrated significant clinical activity and good tolerability in this group of patients. The best response rate was 14%, and 61% achieved stable disease, with median TTP of 7.1 months and OS of 10.2 months. Toxicities were mainly grade 1 or 2, with hand-foot syndrome (73%), diarrhoea (69%), and neutropenia (63%) being the most commonly encountered.

Tivantinib is a selective oral inhibitor of c-Met, the tyrosine kinase receptor for hepatocyte growth factor involved in tumour cell migration, invasion, proliferation, and angiogenesis. Having shown promising results in HCC in phase 1 studies as monotherapy and in combination with sorafenib, a phase 2 multicentre randomised controlled trial involving 107 HCC patients randomised to receive twice daily oral tivantinib 240 or 360 mg or placebo as second-line treatment was conducted.[52] The study met its primary endpoint of improved TTP by central radiological review (1.6 vs. 1.4 months; $p = 0.04$). Adverse events were similar between the treatment arms except for a higher incidence of fatigue and haematological toxicity with tivantinib.

Foretinib is an oral multikinase inhibitor targeting MET, RON, AXL, TIE-2, and VEGFR. The MET111645 study is a phase 1/2 study investigating foretinib as first-line therapy in Asian patients with advanced HCC.[53] Thirteen patients were enrolled in the phase 1 study. Foretinib 30 mg daily appeared to be well-tolerated. A total of 39 patients were treated with foretinib 30 mg daily in the phase 2 study. In total, 22% of patients had partial responses. The disease control rate was 81%. The overall response rate was 24% and median TTP was 4.2 months. Median OS was 15.7 months. These results are promising and suggest that a phase 3 study should be conducted to further evaluate this drug for treatment of HCC.

CONCLUSIONS

Recent advances in treatment modalities for patients with HCC are contributing to the changing landscape for HCC management. Undeniably, these advances have contributed to improved outcomes for this patient group.

Improved safety, as well as long-term outcomes, has expanded the role of hepatic resection for HCC, especially for elderly patients and those with borderline liver function. The advent of minimally invasive techniques has also reaffirmed the role of surgical resection as the treatment of choice for HCC patients.

New modalities of ablation are enhancing its role as a curative treatment for HCC in patients who cannot undergo resection. Even though both these treatment options are associated with relatively high rates of recurrence, there appear to be promising adjuvant therapies in the pipeline that could further improve treatment outcomes.

In patients with unresectable HCC, TACE and radioembolisation are the treatments of choice. Prospective clinical trials should be conducted to compare these two locoregional therapies for HCC. Clinical studies with systemic therapies combined with TACE are ongoing and may improve survival outcomes for this group of patients. It is hoped that combination treatments may result in a higher chance of downstaging of an initially unresectable tumour to become resectable, thus improving the prognosis for these patients. Novel agents targeting the molecular pathways are also being investigated for metastatic HCC.

Taken together, these advances in treatment modalities may well mark the dawn of a new era in the management of patients with HCC.

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