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Hepatology

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ALT: Alanine Aminotransferase CHB: Chronic Hepatitis B; eCrCl: Estimated Creatinine Clearance; ESRD: End Stage Renal Disease

*Comparison of ALT normalization, viral suppression, and impact on renal and bone function were made between tenofovir aladenamide and tenofovir disoproxil fumarate.[1-3]

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4. Vemlidy Prescribing Information. (Version HK-NOV20-US-AUG20).

VEMLIDY® Abbreviated Prescribing Information (Version: HK-NOV20-US-AUG20) Presentation: Tablets: 25 mg of tenofovir alafenamide - yellow, round, film-coated tablets, debossed with "GSI" on one side of the tablet and "25" on the other side. **Indications:** VEMLIDY is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease. **Dosage:** Prior to initiation of VEMLIDY, patients should be tested for HIV-1 infection. VEMLIDY alone should not be used in patients with HIV infection. Adults: The recommended dosage is 25 mg (one tablet) taken orally once daily with food. Patients with Renal Impairment: No dosage adjustment is required in patients with estimated creatinine clearance greater than or equal to 15 mL/min, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL/min) who are receiving chronic hemodialysis. On days of hemodialysis, administer VEMLIDY after completion of hemodialysis treatment. VEMLIDY is not recommended in patients with ESRD who are not receiving chronic hemodialysis. Patients with Hepatic Impairment: No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh A). Not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment. **Contraindications:** None. **Warnings and Precautions:** Severe acute exacerbation of Hepatitis B after discontinuation of treatment: Discontinuation of VEMLIDY, may result in severe acute exacerbations of hepatitis B. Patients who discontinue VEMLIDY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. Risk of development of HIV-1 resistance in patients coinfected with HBV and HIV-1: Due to the risk of development of HIV-1 resistance, VEMLIDY alone is not recommended for the treatment of HIV-1 infection. The safety and efficacy have not been established in patients coinfected with HBV and HIV-1. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VEMLIDY, and, if positive, an appropriate antiretroviral combination regimen that is recommended for patients coinfected with HIV-1 should be used. New onset or worsening renal Impairment: Prior to or when initiating VEMLIDY, and during treatment with VEMLIDY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Lactic acidosis/severe hepatomegaly with steatosis: Treatment with VEMLIDY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Adverse reactions:** Refer to warning and precautions for severe acute exacerbation of hepatitis B, new onset or worsening of renal impairment, and lactic acidosis/severe hepatomegaly with steatosis. Headache, abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea and dyspepsia were reported in ≥ 5% of subjects in clinical studies. **Drug interactions:** Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Antimycobacterial: rifabutin, rifampin, rifapentine. Herbal Products: St. John's wort. Drugs that reduce renal function or compete for active tubular secretion such as acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. **Before prescribing, please consult full prescribing information which is available upon request.** VEMLIDY is a registered trademark of Gilead Sciences, Inc., or its related companies.

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The Cover Shot

The Gorgeous Scenery in Hong Kong Contributes to the Fight Against Steatotic Liver Disease

After walking past the Sharp Peak (aka Nam She Tsim) in Sai Kung, the stunning mountainscapes of the Sai Kung East Country Park, and the breath-taking panorama of four beaches - Tung Wan Beach, Tai Wan Beach, Ham Tin Beach and Sai Wan Beach are revealed. Such gorgeous scenery in Hong Kong is now my motivation for the fight against fatty liver disease. Aerobic exercise, including hiking, brisk walking, cycling, jogging, etc., is beneficial to prevent or even regress fatty liver disease. I encourage our friends and colleagues, as well as our patients, to go hiking regularly to protect ourselves from fatty liver disease.

Prof Grace LH WONG
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The New Landscape of Hepatology

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Issue Editor

Prof Henry LY CHAN

In the past 20 years, we have experienced a dramatic evolution in the landscape of Hepatology. Viral hepatitis B has been the major cause of liver-related morbidity and mortality in Hong Kong ever since HBsAg was discovered in the 1960s. Over 80 % of liver cirrhosis and hepatocellular carcinoma (HCC) are related to chronic hepatitis B virus (HBV) infection. The development of nucleot(s)ide analogues has provided a once daily oral treatment for HBV. The current first-line HBV drugs, namely entecavir, tenofovir alafenamide, and tenofovir disoprovil fumarate, are highly effective in suppressing the replication of HBV with minimal risk of drug resistance. Viral hepatitis C treatment has advanced at lightning speed, taking less than 30 years from disease discovery to the availability of a cure. Nowadays, the combination of oral antiviral drugs for 8 - 12 weeks can secure a hepatitis C viral cure rate of 99 %. In view of the vast health hazard of viral hepatitis infections and the availability of effective antiviral treatments, the World Health Organization has set a goal of eliminating viral hepatitis as a major public health threat by 2030[1]. Hong Kong government has responded by setting up a steering committee co-led by the Chief Executive of the Hospital Authority and Director of Health since 2017 to coordinate a territory-wide effort in viral hepatitis elimination.

Although we start to see the end of the tunnel for viral hepatitis, fatty liver disease has emerged as an increasingly important health problem. The prevalence of non-alcoholic fatty liver disease (NAFLD) is estimated to be approximately 30 % in Hong Kong as well as in other parts of the world. With an increasing trend of obesity, the global incidence of NAFLD is also expected to climb in the coming years. Complications of NAFLD have overtaken viral hepatitis in the West as a major cause of liver transplantation. NAFLD is closely associated with metabolic syndrome. The prevalence and severity of fatty liver disease are much higher in patients with type 2 diabetes mellitus as compared to the general population. Recently, the hepatology community has proposed to change the nomenclature of NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD)[2]. The new nomenclature aims to define positive diagnostic criteria based on evidence of hepatic steatosis, in addition to one of the following three criteria, namely overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. New drugs are under development for fatty liver disease with the primary target of halting or regressing the development of liver fibrosis.

With advances in understanding and treatment of viral hepatitis, the age-standardised rate and mortality of HCC in Hong Kong have been on gentle declining slopes over the past decade. Nonetheless, liver cancer has stood firm as one of the top 5 cancer mortality in Hong Kong[3]. Liver cancer surveillance is of pivotal importance among patients at risk of HCC, as the prognosis of HCC is largely correlated with the size of the tumour. Hepatic resection remains the mainstay of curative treatment for early HCC, whereas combination immune therapy has become the new hope for patients with advanced HCC.

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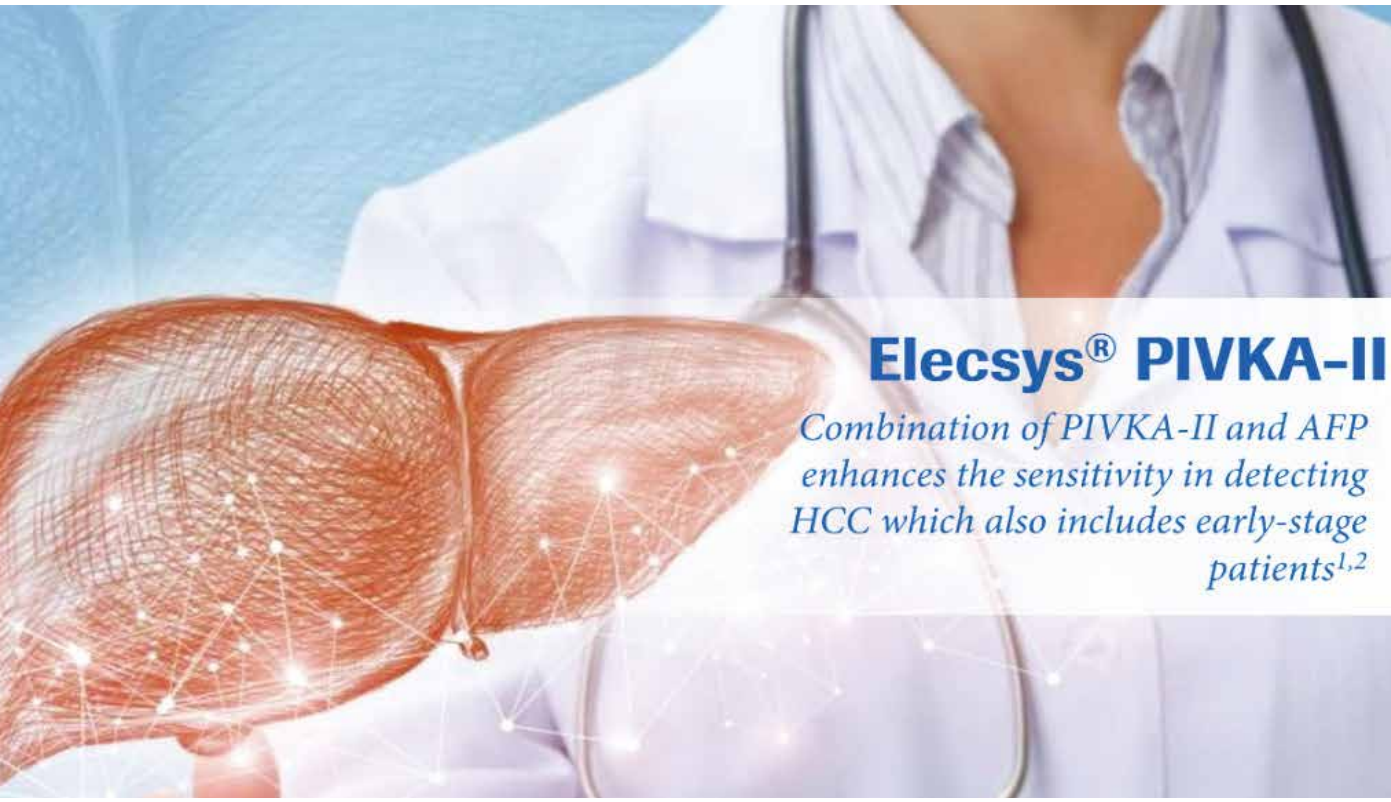

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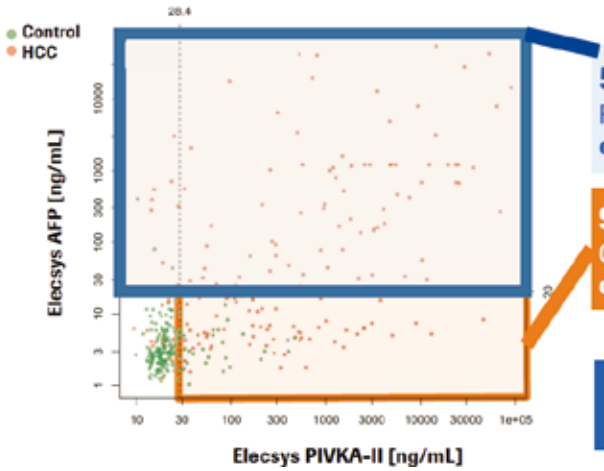

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AFP ≤20 ng/mL	14	67	81
Total	22	146	**168**

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The Role of Novel Viral Biomarkers in Management of Chronic Hepatitis B Infection

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BACKGROUND

Chronic hepatitis B (CHB) infection affects 316 million people globally, and affects 6.2 % of the population in Hong Kong[1]. CHB is the leading cause of cirrhosis and hepatocellular carcinoma (HCC), which is the 5th commonest cancer and is the 3rd most lethal cancer in Hong Kong. The majority of people with CHB were infected during the perinatal period or early childhood[2] when they were susceptible to the chronicity of the infection due to a less mature host immune system. Once chronicity is established, hepatitis B virus (HBV) remains in the liver for life in the majority of infected subjects.

STANDARD OF CARE

Current first-line antiviral treatment can reduce, but not eliminate, the risk of HCC and cirrhosis. In general, NUCs are indicated for patients with evidence of active hepatic inflammation and/or significant liver fibrosis resulting from viral replication. Locally, all three first-line oral nucleoside analogues (NUCs) are available, which include entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide. For patients at risk of HCC (i.e., male > 40 years old, or female > 50 years old, or family history of HCC, or presence of cirrhosis), regular ultrasound scan of the liver combined with serum alpha feto-protein monitoring every six months is needed for HCC surveillance, regardless of whether NUC has been prescribed.

The cascade of care in CHB highlights the different levels of cure or treatment endpoints (Fig. 1). On-treatment virological suppression, also known as incomplete cure, is the most reachable endpoint and can be achieved in > 90 % of NUC-treated subjects. Partial cure is defined as off-therapy virological suppression with a low hepatitis B surface antigen (HBsAg) level (< 100 IU/mL), which is observed in around 20 % of subjects who received a finite course of therapy. Functional cure refers to sustained HBsAg seroclearance plus ≥ six months unquantifiable HBV DNA[3], which is associated with improved clinical outcomes but is only achieved by ~ 1 % antiviral-treated subjects annually[4]. Complete cure is defined as eradication of cccDNA, and sterilising cure is defined as clearance of integrated DNA; both of which are unreachable with the current treatments. With these considerations, functional cure is regarded as the desirable treatment endpoint and has become a benchmark for phase 3 clinical trials of novel CHB therapy, with a threshold of HBsAg loss ≥ 30 % as an arbitrarily acceptable rate of response six months after cessation of investigational compounds[5].

WHY VIRAL BIOMARKERS ARE NEEDED AND HOW ARE THEY BEING USED?

Theoretically, to assess treatment candidacy, evaluate therapeutic effects and predict the risk of liver-related events, liver biopsy is the 'gold standard' which can be used to assess histological hepatic inflammation and fibrosis, as well as to quantify transcriptionally active intrahepatic covalently closed circular DNA (cccDNA). However, liver biopsy is invasive in nature and can cause serious complications such as significant haemorrhage, pneumothorax, or biliary sepsis. In addition, there are concerns for sampling error, intra/inter-observer variability and lack of standardisation of cccDNA quantification. These render liver biopsy for cccDNA quantification to remain as a research tool[6]. To this end, a number of blood-based HBV biomarkers have been studied as surrogate markers for cccDNA. Well established markers such as HBV DNA, qualitative hepatitis B e antigen (HBeAg) and qualitative HBsAg have been incorporated in many guidelines as part of the diagnostic workup to decide the phase of CHB. The natural phases of CHB infection include HBeAg-positive chronic infection (previously known as 'immune-tolerant phase'), HBeAg-positive chronic hepatitis B (previously known as 'immune-clearance phase'), HBeAg-negative chronic hepatitis B, HBeAg-negative chronic infection (also known as; inactive carriers), and HBsAg seroclearance[7, 8].

HBV DNA is perhaps the most well-known and clinically utilised viral biomarker in CHB infection. The vast majority of detectable serum circulating HBV DNA is in the form of enveloped/encapsidated rcDNA[9]. The level of HBV DNA varies with different phases of infection, with higher levels in HBeAg-positive patients and lower levels in HBeAg-negative patients. In untreated CHB, HBV DNA shows a moderate correlation with intrahepatic cccDNA (correlation coefficient up to 0.49)[10]. The widely used in vitro nucleic acid amplification method allows high sensitivity of DNA detection and quantification, with lower limits reaching or below 1 to 2 log. NUCs are usually indicated if serum HBV DNA is > 2,000 - 20,000 IU/mL accompanied by raised serum alanine aminotransferase, a marker of hepatic necroinflammation. In special populations such as pregnancy, the cut-off above which antiviral treatment is indicated varies from the general considerations[11].

The qualitative HBeAg is used to stratify the disease phase and as an endpoint of treatment among

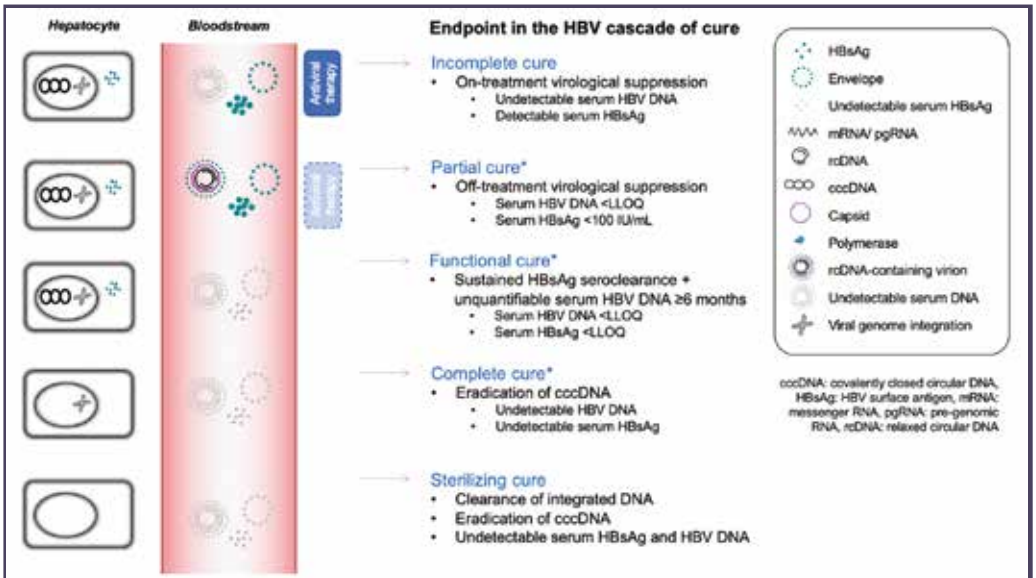

*Fig. 1: Treatment endpoints in the cascade of cure in chronic hepatitis B infection. cccDNA, covalently closed circular DNA; HBsAg, hepatitis B surface antigen; mRNA, messenger RNA; pgRNA, pre-genomic RNA; rcDNA, relaxed circular DNA; HBV, hepatitis B virus; DNA, double-strand¬ed deoxy-ribonucleic acid. *Definitions highlighted in the revised treatment endpoint guidance. Adapted from Mak LY et al. Clin Mol Hepatol 2023; 29:263-276 – an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License.*

HBeAg-positive patients (i.e., HBeAg seroclearance or seroconversion). In contrast, the quantitative HBeAg levels are mainly for research purposes, which can be quantified and expressed in Paul-Ehrlich Institute unit per mL (PEI-U/mL).

Quantitative HBsAg (positive or negative) is essential to diagnose HBV infection. Chronicity of HBV infection is arbitrarily defined as persistent seropositivity for HBsAg for > six months. In comparison, quantitative HBsAg (qHBsAg) is a measure of the rate of viral protein production (from translation) and indirectly reflects the viral reservoir. qHBsAg can inform whether the treatment endpoint for CHB has been reached and allows risk prediction for various clinical outcomes (see below). The lower limit of detection is around 0.05 IU/mL for most commonly used quantitative assays. The majority of HBsAg detected in the serum are subviral particles (SVP), which exceed mature virions by 100 - 100,000 times[12]. Serum HBsAg can be produced from either cccDNA or integrated DNA[13], with the latter contributing more in HBeAg-negative patients.

NOVEL VIRAL BIOMARKERS

HBV RNA and hepatitis B core-related antigen (HBcrAg) are two novel serum-based viral biomarkers that have been extensively evaluated in CHB. Circulating HBV RNA are encapsidated pgRNA in virus-like particles[14]. In untreated patients, it shows an excellent correlation with intrahepatic cccDNA (correlation coefficient up to 0.89)[15]. Prior to antiviral treatment, serum HBV pgRNA levels are always 1 - 2 log lower than serum HBV DNA. HBcrAg is a composite of 3 related proteins that share an identical 149 amino acid sequence: hepatitis B core antigen, HBeAg and a truncated 22 kDa precore protein (p22Cr) that is a processed product of the precore protein. HBcrAg demonstrates a good correlation with intrahepatic cccDNA (correlation coefficient up to 0.70) in both untreated and NUC-treated subjects[16]. These two biomarkers have been studied to predict the risk of liver-related events in CHB, including both good outcomes (achieving HBV cure) and bad outcomes (i.e., HCC).

Predicting HBV Cure

In view of the low incidence of HBsAg seroclearance, most patients need to take NUCs on a long-term basis to prevent off-treatment virological relapse. Interestingly, it has been reported that virological flare from NUC discontinuation has been associated with a higher rate of functional cure, which has laid the ground for the 'stop-to-cure' approach that hypothesised that virological rebound upon NUC cessation can act as an 'auto-vaccination effect' and lead to immune reinvigoration[17]. Numerous studies have explored predictors for successful discontinuation of NUCs to achieve incomplete cure, partial cure or even functional cure. Low end-of-therapy (EOT) serum qHBsAg, preferably < 100 IU/mL, has been consistently shown to predict partial cure[18]. In addition, low EOT serum HBcrAg, undetectable EOT serum HBV pgRNA, or a combination of both, identified a subgroup of patients who would be able to stop long-term NUC with a lower chance of flare[19]. Some patients with a favourable viral biomarker profile would benefit from such an approach and achieve a functional cure. In fact, assessing viral biomarkers (serum HBcrAg and pgRNA) as early as week 4 of NUC treatment is able to highlight a group of patients who would achieve a low serum qHBsAg (< 100 IU/mL) or HBsAg seroclearance in the long run[20]. This approach can help to identify subjects during the early phase who should not stop NUC and should be prioritised in clinical trials. HBcrAg and qHBsAg have

been incorporated into Japanese guidelines to predict off-therapy virological relapse[21].

Nevertheless, the 'stop-to-cure' approach is not applicable to all patients depending on ethnicity, liver reserve, and viral burden assessment. Guidelines recommend that long-term NUC might be discontinued only if the duration of NUC is long enough, in the absence of cirrhosis, and if the patient can comply with frequent off-therapy monitoring to detect flare. Moreover, the 'stop-to-cure' approach is more likely to be successful in Caucasian patients than Asian patients, even if they demonstrate the same viral biomarker profile. For patients with CHB in Hong Kong, the bottom line is that once NUCs are started, they should be maintained on a long-term basis except two situations: 1) the patient is deliberately recruited for the 'stop-to-cure' approach in a clinical trial setting or 2) the patient has achieved functional cure, and there is no evidence of cirrhosis.

Predicting HCC

Traditional viral biomarkers (HBV DNA and HBsAg) give important clues to the risk of HCC among treated CHB subjects. Serum qHBsAg has been shown to be associated with HCC risk. The hazard ratio for developing HCC was 13.7 for low viremic (HBV DNA < 2,000 IU/mL) HBeAg-negative patients with serum qHBsAg ≥ 3 log compared to those with serum qHBsAg < 3 log[22]. Moreover, HBsAg seroclearance, i.e., functional cure, is associated with significantly reduced HCC risk, especially in subjects who achieved this endpoint before the age of 50 and, regardless of whether the patient was given antiviral therapy[23]. Serum viral load (HBV DNA) is a well-known risk factor for HCC and demonstrated a biological gradient in the REVEAL-HBV cohort[24]. Long term NUC treatment has been shown to reduce the risk of HCC[25].

Since HBV DNA is no longer detectable in the serum (in the majority of cases) upon NUC treatment, and the fact that qHBsAg only declines modestly upon NUC, other viral biomarkers have been explored to assess the risk of HCC in antiviral-treated CHB patients. In this context, serum HBcrAg and pgRNA might aid risk stratification in addition to serum HBV DNA and qHBsAg levels[26, 27]. While serum HBcrAg is reduced in all NUC-treated CHB patients[28], a high post-treatment HBcrAg was associated with > 2 fold increase in risk of HCC[29]. Similarly, on-treatment detectable serum pgRNA is associated with 3.5-fold higher risk of HCC in 2 years' time[30].

WHY ARE NOVEL VIRAL BIOMARKERS NOT IN CLINICAL USE?

Both HBcrAg and HBV pgRNA are largely used in the research context. The main limitation with HBcrAg is the relatively high lower limit of detection (3 log U/mL), and it is not detectable in up to 30 % of HBeAg-negative patients[31]. HBV pgRNA quantification is procedurally more complicated than HBcrAg measurement. While the performance of RNA assays has recently been improved to approach the World Health Organization standards, the methodology and assays for pgRNA measurement need standardisation. Lastly, data for novel viral biomarkers mainly originated from Asian patients in single-centre studies. External validation is needed to confirm the profile and performance characteristics of these biomarkers in every subgroup of patients with CHB.

CONCLUSION

Viral biomarker assessment is indispensable in the clinical management of patients with CHB. In the current era with highly effective NUC therapy as the mainstay of treatment, HBV DNA will be expected to be undetectable and novel viral biomarkers can provide further insights into treatment efficacy. These include hepatitis B core-related antigen (HBcrAg) and HBV RNA, both of which have shown potential to evaluate treatment endpoints and predict the risk of HCC. As of now, both novel biomarkers are largely used in studies as a research-basis but are not ready yet to be used directly in patient management. Optimisation of assay sensitivity, standardisation of assays and validation studies are needed before these biomarkers can be broadly implemented in clinical use.

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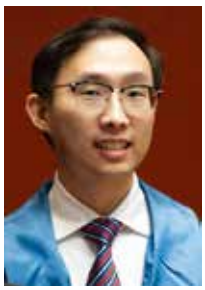
Radiology Quiz

Dr Wisely HH TANG
MBBS, FRCR



Dr Wisely HH TANG

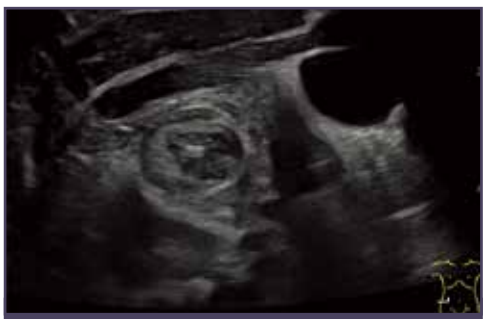


Fig. A

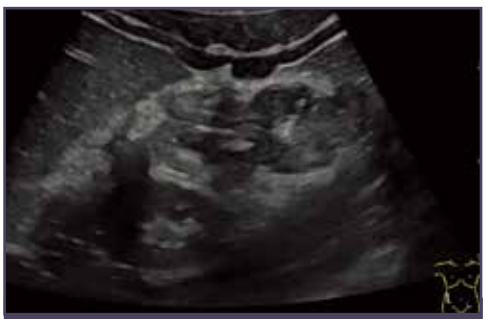


Fig. B

History:
A 2-year-old boy presenting with abdominal pain.

Questions

1. What are the abnormalities in the ultrasound study?
2. What is the most likely diagnosis?
3. What is the next step of management?

(See P.32 for answers)

Current and Future Treatments for Metabolic Dysfunction-associated Fatty Liver Disease

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Dr Vincent Wai-sun WONG

This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2024.

INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD), also known as nonalcoholic fatty liver disease and metabolic dysfunction-associated steatotic liver disease, affects around 30 % of the Asian adult population and is projected to become one of the leading causes of cirrhotic complications and hepatocellular carcinoma by 2030[1, 2]. Lifestyle intervention in terms of a healthy diet and regular exercise remains the cornerstone for the management of MAFLD, with a 5 - 7 % and > 10 % weight reduction typically quoted as required for resolution of metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis improvement, respectively[3, 4]. Nonetheless, few patients can achieve such weight reduction targets, and even fewer can maintain them in the long run[5]. Therefore, some patients with MAFLD will need pharmacological treatments. This short review focuses on existing off-label treatments for MASH and promising agents in the pipeline (Table 1).

SELECTION PATIENTS FOR TREATMENT AND ASSESSMENT OF TREATMENT RESPONSE

Current guidelines are in agreement that pharmacological treatment of MASH should be reserved for patients with MASH (defined by the presence of hepatic steatosis, lobular inflammation and hepatocyte ballooning) and significant fibrosis (i.e., stage 2 fibrosis or higher)[6 - 8]. Unfortunately, there are no readily available and reliable biomarkers for MASH. In clinical practice, noninvasive tests of fibrosis such as vibration-controlled transient elastography or blood fibrosis biomarkers are often used to identify patients with significant liver disease instead[9].

At the end of the day, what is important to the patients is a reduction in adverse liver outcomes and mortality. However, as liver outcomes take too long to develop, regulators agreed that histological response (MASH resolution without worsening of fibrosis and/or fibrosis improvement without worsening of MASH) may serve as surrogate endpoints for conditional drug approval[10]. Again, it would be important to define how to use noninvasive tests to assess treatment response.

CURRENTLY AVAILABLE OFF-LABEL TREATMENTS

At present, there is no registered treatment for MASH. However, vitamin E and pioglitazone have been shown in a number of clinical trials to reduce both hepatic steatosis and inflammation and are thus recommended by current guidelines as possible treatments in selected patients with MASH[11, 12].

Vitamin E works by its anti-oxidant action. It is given orally at a dosage of 800 IU per day. Apart from the histological response described above, a retrospective propensity score-matching analysis suggested that vitamin E could reduce hepatic decompensation and increase transplant-free survival in patients with MASH and F3-F4 fibrosis[13]. Contrary to most MASH drugs, vitamin E has a neutral effect on body weight and the metabolic profile. The drug is generally well tolerated, but some conflicting data suggest a potential small increase in the risk of prostate cancer and intracranial haemorrhage.

Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist registered for the treatment of type 2 diabetes. It is an insulin sensitiser that reduces ectopic fat deposition in internal organs. Despite robust data on histological improvements, there are no good studies on clinical outcomes except a retrospective study from Hong Kong indicating that the drug was associated with a reduction in hepatocellular carcinoma and cirrhotic complications in patients with chronic hepatitis B and type 2 diabetes[14]. Pioglitazone is associated with modest weight gain, fluid retention and increased bone loss. Some studies suggest a small increase in the risk of bladder cancer, but data are inconsistent[15].

The biggest advance in obesity medicine in the past decade is the development of glucagon-like peptide-1 receptor agonists (GLP-1RAs). In particular, liraglutide and semaglutide have been registered for the treatment of both type 2 diabetes and obesity. GLP-1RAs reduce the appetite and slow down gastric emptying. The resultant reduction in food intake leads to weight reduction of up to 5 - 15 % in different studies. In a phase 2b study, semaglutide at a dose of 0.4 mg daily given subcutaneously for 72 weeks resulted in MASH resolution with no worsening of fibrosis in 59 % of

Table 1. Existing and future treatments for metabolic dysfunction-associated steatohepatitis. (Developed by author)

Drug	Mechanism	MASH resolution	Fibrosis improvement	Remarks
Existing drugs				
Vitamin E	Anti-oxidant	Yes	Modest at best	May increase intracranial haemorrhage and prostate cancer
Pioglitazone	PPAR-gamma agonist	Yes	Modest at best	May cause fluid retention, weight gain, bone loss and bladder cancer
Liraglutide and semaglutide	Glucagon-like receptor agonists	Yes	Modest at best	Requires subcutaneous injection; common gastrointestinal side effects include nausea and vomiting, constipation and diarrhoea
Drugs in the pipeline				
Resmetirom	Thyroid hormone receptor-beta agonist	Yes	Yes	May cause mild nausea and diarrhoea
Lanifibranor	Pan-PPAR agonist	Yes	Yes	May cause fluid retention and weight gain
Efruxifermin and pegozafermin	Fibroblast growth factor 21 analogues	Yes	Yes	Requires subcutaneous injection; may cause nausea and diarrhoea

MASH, metabolic dysfunction-associated steatohepatitis; PPAR, peroxisome proliferator-activated receptor

patients, but there was no significant increase in fibrosis improvement[16]. Nonetheless, in another study in patients with compensated MASH-related cirrhosis, semaglutide did not increase the rate of MASH resolution or fibrosis improvement, suggesting that the drug might be too late for patients with advanced liver disease[17]. GLP-1RAs can cause nausea and vomiting, altered bowel habits and injection site reactions, and up to 10 - 20 % of patients may need treatment cessation. Careful titration of GLP-1RAs, starting at a lower dose, can improve tolerance and treatment adhesion. The ongoing phase 3 ESSENCE trial (NCT04822181) aims to establish semaglutide as a treatment for non-cirrhotic MASH.

TREATMENTS IN THE PIPELINE

In the past few years, a few agents have shown promising results in phase 2 and 3 clinical trials.

Resmetirom, a liver-specific thyroid hormone receptor-beta agonist, achieved both regulatory histological endpoints in the phase 3 MAESTRO-NASH study[18]. At an oral dose of 100 mg daily, resmetirom led to resolution of MASH with no worsening of fibrosis in 30 % of patients and fibrosis improvement with no worsening of MASH in 26 % after 52 weeks of treatment. In the accompanying phase 3 MAESTRO-NAFLD-1 study based on noninvasive assessments alone, resmetirom was superior to placebo in reducing hepatic fat, liver stiffness, low-density lipoprotein-cholesterol, apolipoprotein B and triglycerides[19]. The drug was well tolerated, with only mild nausea and diarrhoea reported by some patients. There was no increase in heart rate, blood pressure or cardiovascular events in all development programmes, confirming the hepatic specificity of thyroid hormone receptor agonism. It is anticipated that resmetirom will become the first drug to be registered for the treatment of MASH.

Lanifibranor, a pan-PPAR agonist, achieved MASH resolution with no worsening of fibrosis in 49 % and fibrosis improvement with no worsening of MASH in 48 % of patients at a dose of 1,200 mg daily for 24 weeks in the phase 2b NATIVE study[20]. Similar to other PPAR-gamma agonists, lanifibranor resulted in mild oedema and weight gain. The risk of bone loss and bladder cancer needs to be examined in larger studies with long-term follow-up. The phase 3 NATiV3 trial for non-cirrhotic MASH is ongoing (NCT04849728).

Fibroblast growth factor (FGF)-21 analogues (e.g., efruxifermin and pegozafermin) are a new class of drugs that have attracted much attention in recent years. Even short-term early phase studies demonstrated potentially robust effects on MASH resolution and fibrosis improvement[21, 22]. These promising data require validation in larger studies.

Furthermore, even though GLP-1RAs have revolutionised the management of obesity and type 2 diabetes, the field is already moving towards dual and triple agonists targeting not only GLP-1 but also glucose-dependent insulinotropic polypeptide (e.g., tirzepatide) and/or glucagon receptors (e.g., retatrutide) simultaneously. These dual and triple agonists are more effective than GLP-1RAs alone in reducing body weight and glycated haemoglobin[23, 24]. It would be interesting to see if these new agents are also more effective in the management of MASH, especially in patients with advanced liver disease.

CONCLUSIONS

Efforts in basic and clinical research have led to effective treatments for MASH. It is likely that clinicians can choose from one or more agents in the next few years according to the clinical profile, comorbidities, and patient preference. Several questions remain, though. First, histological endpoints are surrogates after all. The field needs to prove that treatments would improve liver-related outcomes and, preferably, overall mortality. Second, it is unrealistic to perform liver biopsies to select patients for treatment and assess treatment response. The approval of MASH treatments must be accompanied by clear guidance on the use of noninvasive tests. Moreover, an effective treatment for MASH-related cirrhosis, a condition needing treatment most urgently, remains elusive. Finally, because of considerable heterogeneity among patients, knowledge of factors associated with treatment response (including but not limited to demographics, metabolic profile,

markers of liver disease activity, and genetics) will be needed to achieve the ultimate goal of precision medicine in MASH.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Current and Future Treatments for Metabolic Dysfunction-associated Fatty Liver Disease" by Prof Vincent Wai-Sun WONG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or answer link: https://forms.gle/tp9yh1w9ZEq1uUdx5 or by mail to the Federation Secretariat on or before 30 April 2024. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/Fl., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

Questions 1 - 10: Please answer T (true) or F (false)

1. **Metabolic dysfunction-associated steatotic liver disease (MASLD) currently affects 10 % of the adult population in Asia.**
2. **Most patients with metabolic dysfunction-associated steatohepatitis (MASH) can achieve improvement in liver fibrosis through 3 - 5 % weight reduction.**
3. **MASH is defined as the presence of hepatic steatosis, lobular inflammation and hepatocyte ballooning on liver biopsy.**
4. **Vitamin E improves hepatic necroinflammation in MASH through its anti-oxidant action.**
5. **Pioglitazone improves hepatic necroinflammation in MASH through mild to moderate weight reduction.**
6. **A "top-down approach" of starting glucagon-like peptide-1 receptor agonists at its top dose followed by down-titration according to response and tolerability will lead to maximal therapeutic response for both weight reduction and resolution of MASH.**
7. **Semaglutide, a glucagon-like peptide-1 receptor agonist, failed to increase the rates of MASH resolution and fibrosis improvement in patients with compensated MASH cirrhosis.**
8. **Resmetirom, a liver-specific thyroid hormone receptor-beta agonist, increased the rates of MASH resolution and fibrosis improvement without obvious cardiovascular toxicity in the phase 3 MAESTRO-NASH study.**
9. **Lanifibranor is a new specific peroxisome proliferator-activated receptor-gamma agonist with superiority to pioglitazone in achieving MASH resolution.**
10. **Tirzepatide is a dual agonist of the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptors. It is highly efficacious in reducing body weight and improving glycemic control in patients with type 2 diabetes.**

ANSWER SHEET FOR APRIL 2024

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2024 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Current and Future Treatments for Metabolic Dysfunction-associated Fatty Liver Disease

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State Key Laboratory of Digestive Disease, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong

Answer Link

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

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Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to March 2024 Issue

Surgical Treatment of Adult Diabesity

1. F 2. T 3. T 4. T 5. F 6. T 7. T 8. T 9. T 10. T

Imaging of Liver Nodules

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IMAGING OF LIVER NODULES

The imaging of liver nodules is a common clinical problem, and most liver nodules are discovered via screening programmes (such as for hepatitis B carriers), health checks or incidental findings from imaging of unrelated clinical problems[1]. Multiphasic contrast enhanced CT and multiphasic contrast enhanced MRI scans of the liver are helpful in characterisation of indeterminate nodules detected on ultrasound, while contrast enhanced PET-CT scans may offer information regarding the metabolic activity of liver nodules and allow for comprehensive whole body disease staging if malignancy is identified.

The main roles of imaging in the management of liver nodules include:

1. Distinguish between benign and malignant liver nodules
2. Monitoring of change.
3. Guide biopsy and treatment of lesion (such as in thermal ablation).
4. Staging of disease.

An understanding of the imaging features of common liver nodules and the limitations of imaging by clinicians is paramount in managing liver nodules. In this article, the imaging features of commonly encountered liver nodules will be reviewed and limitations in imaging will be highlighted.

Commonly encountered liver nodules to be discussed are benign lesions, including benign cysts, haemangiomas, focal nodular hyperplasia, hepatic adenomas and dysplastic nodules; and malignant lesions, including primary tumours of the liver (such as hepatocellular carcinoma and cholangiocarcinoma) and liver metastases.

BENIGN CYSTS

These are considered developmental and are usually rounded or lobulated thin-walled lesions or thin walled septated lesions. They are usually well characterised on ultrasound and do not require follow-up.

On ultrasound, simple cysts are typically anechoic or hypoechoic with thin or imperceptible walls, showing posterior acoustic enhancement from increased through transmission. They typically appear with low attenuation on CT, high signal on T2 and low signal on T1 on MRI with no contrast enhancement.

The main challenge of imaging liver cysts is the differentiation from other cystic lesions – including infective, neoplastic and post-traumatic liver lesions. The presence of wall thickening, soft tissue components and complicated content should prompt further imaging assessment with CT or MRI[2].

HAEMANGIOMAS

Hemangioma is the most common benign liver tumour and is more common in female subjects (F:M ratio 5:1)[3]. They are thought to be congenital, receive blood supply from the hepatic artery and are usually peripheral in location. The cavernous type is the most common.

On ultrasound, the lesions are typically well circumscribed and echogenic. They may have the echogenic rim and hypoechoic centre. CT and MRI typically show discontinuous (often globular) peripheral enhancement on the arterial phase, progressive contrast enhancement on the portal venous phase and complete contrast 'filling in' on the delayed phase. They are often moderately high signals on T2 on MRI[4, 5]. They may show restriction to diffusion on diffusion weighted imaging due to slow flow[6]. A word of caution when using liver specific contrast agents for MRI imaging (such as Primovist) when the appearance of haemangiomas can be variable in the delayed phases. In particular, high flow haemangiomas can show 'pseudo washout', caused by increased contrast agent uptake in adjacent liver cells, and needs to be distinguished from true contrast washout in hepatocellular carcinoma[7].

The typical contrast enhancement pattern of haemangioma, considered the most specific imaging feature of liver haemangioma, is not always seen, and reports exist of contrast 'filling in' being seen in other liver lesions such as liver abscesses and hepatocellular carcinoma[8].

FOCAL NODULAR HYPERPLASIA

Focal nodular hyperplasia is the second most common benign liver tumour. They have a strong female predilection (F:M ratio 8:1). They are benign lesions of hepatocyte hyperplasia in a background of normal or nearly normal liver that have a central scar with radiating fibrous septa and a central supplying artery with 'spoke-whee' pattern of branching vessels.

On ultrasound, the appearances are variable. Some lesions are isoechoic, making their detection on ultrasound difficult, while others may be better

circumscribed and more detectable. Multiphasic contrast enhanced CT or MRI are usually better for detecting focal nodular hyperplasia with lesions typically showing avid arterial phase enhancement, with sustained enhancement on portal venous phase and delayed phase similar to adjacent liver parenchyma. On MRI, the lesions are hypointense/isointense on T1 and isointense/hyperintense on T2, while the central scars are hypointense on T1, and hyperintense on T2 and may show delayed contrast enhancement. These lesions can easily be missed if arterial phase imaging is not performed on CT and MRI[9, 10].

HEPATIC ADENOMAS

These lesions have traditionally been thought to be found in young women on oral contraceptives. More recent literature shows increasing incidence in men associated with the use of anabolic steroids, obesity, diabetes mellitus and metabolic syndromes.

These lesions have variable appearances on imaging as they may contain fat, and internal haemorrhage may occur, leading to calcification.

On ultrasound, these lesions tend to be circumscribed, may be hypoechoic or hyperechoic (especially when fat is present) and may have a hypoechoic halo from fatty sparing around the lesion. Posterior shadowing may be seen if calcification is present. On CT, lesion attenuation would depend on content. They show avid arterial phase imaging and become isodense with the liver in the delayed phase. On MRI, they may be hypointense, isointense or hyperintense on T1 (especially if there is fat content or haemorrhage). They may be mildly hyperintense on T2 or hypointense/heterogeneous if there is internal haemorrhage. The out phase signal drops off on in/out phase imaging and may be seen if the lesion contains fat. They show early arterial phase enhancement and may become isointense on portal venous and delayed phase imaging[10, 11].

DYSPLASTIC NODULES

These nodules are seen in cirrhotic liver and have the potential for malignant transformation. They demonstrate cellular atypia and may contain fat. They are broadly classified into low grade dysplastic nodules, which resemble regenerative nodules and high-grade dysplastic nodules, which resemble well differentiated hepatocellular carcinoma[12].

These nodules may not be visible on ultrasound as separate from the cirrhotic changes. Some may be visible as hyperechoic nodules with increased fat content. On CT, they may be of low attenuation (if there is increased fat content) or isodense to the liver on the unenhanced scan. The high-grade dysplastic nodules may show early arterial phase enhancement and may become isodense to the liver on the portvenous phase. The delayed phase may show no contrast washout. On MRI, dysplastic nodules may show hyperintensity on T1 and show out phase signal drop off on in/out phase imaging in fat containing nodules. They tend to be isointense/hypointense on T2 and hypointense on diffusion weighted imaging. High grade nodules may show early arterial phase enhancement and become isointense with the liver on the portal venous phase and delayed phases. When the liver specific contrast agent is used, high grade dysplastic nodules may appear hypointense on the hepatobiliary phase at 20 minutes[12-14].

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is the most common primary liver cancer, and the incidence is particularly high in areas like Hong Kong, where the endemic rate of Hepatitis B is high. It is highly associated with liver cirrhosis from both viral and alcoholic causes. Liver cancer is the third most common cause of cancer related death worldwide, according to WHO[15].

Hepatocellular carcinomas derive blood supply from hepatic arteries rather than the portal vein. They may present as unifocal, multifocal or diffuse forms. They have a propensity to invade portal vein and hepatic vein branches, and tumour thrombus may be present.

On ultrasound, most hepatocellular carcinomas are mildly hypoechoic compared with adjacent liver, while some are isoechoic and a minority are hyperechoic. They can be extremely difficult to detect on ultrasound, especially amidst background cirrhotic changes. On CT, they tend to be hypodense/isodense, showing early arterial phase enhancement with contrast washout on the portovenous and delayed phases. On MRI, T1 signal is variable, while they tend to be mildly hyperintense on T2. They may show restriction to diffusion. They are usually contrast enhancing and hypervascular. Rapid contrast washout, is seen in the majority of hepatocellular carcinomas and this feature is highly specific for hepatocellular carcinoma. Persistent enhancement of the tumour capsule may ensue in the portovenous phase and the delayed phase. Central necrosis may be present. When the liver specific contrast agent is used, hepatocellular carcinomas are hypointense on the hepatobiliary phase at 20 minutes[10, 13, 14, 16].

A scoring system, the LI-RADS system, has been developed to assess the likelihood of hepatocellular carcinoma. The details of the system are beyond the scope of this article, but suffice it to say that some of the aforementioned imaging features are used as major diagnostic criteria[17].

Dual tracer PET-CT scan using C11-acetate and F18-fluorodeoxyglucose (FDG) is very useful in diagnosing and staging hepatocellular carcinoma. F18-FDG tend to detect the poorly differentiated hepatocellular carcinomas, while C11-acetate tend to detect the well differentiated hepatocellular carcinomas. The combination of these isotopes improves the sensitivity for detection (up to 100 % previously reported)[18]. It must be pointed out, however, that tracer uptake is also seen in benign conditions - such as C11-acetate uptake is expected in focal nodular hyperplasia and therefore, dual tracer PET-CT may not be helpful in the distinction between hepatocellular carcinoma and focal nodular hyperplasia.

CHOLANGIOCARCINOMA

Cholangiocarcinoma is the second most common

primary liver cancer, and the tumour arises from the biliary tree (excluding the gallbladder and the Ampulla of Vater). Recurrent pyogenic cholangitis is an important risk factor in Southeast Asia. Other risk factors include Caroli disease, choledochal cyst, choledocholithiais, primary sclerosing cholangitis, cirrhosis, viral infections, inflammatory bowel disease and liver fluke infestation.

Most of these tumours are extrahepatic in the perihilar region proximal to the origin of the cystic duct, while others are seen in intrahepatic locations and in the common bile duct distal to the cystic duct. They may be mass forming and show periductal infiltration or intraductal infiltration.

On ultrasound, cholangiocarcinomas tend to be of intermediate echogenicity, and hypoechoic haloes may be present. Capsular retraction may be present, which gives irregular borders, distinguishing them from other liver tumours. Duct dilation proximal to the cholangiocarcinoma may be seen and intraductal tumour infiltration may be evident. On CT, cholangiocarcinomas tend to be hypodense on the unenhanced scan and show peripheral contrast enhancement with gradual centripetal enhancement on the delayed phase. Associated calcification and duct dilation may be present. On MRI, cholangiocarcinomas tend to be hypointense on T1 and hyperintense on T2. The enhancement characteristics are similar to those seen on CT. The periportal and intraductal infiltration by cholangiocarcinomas are better depicted on MRI, making MRI the imaging modality of choice for assessment of cholangiocarcinomas[16, 19]. Cholangiocarcinomas typically show increased uptake to F18-FDG on PET-CT[18].

LIVER METASTASES

Liver metastases are far more common than primary liver malignancies. Common primary carcinomas that metastasise to the liver include colorectal carcinoma, gastric carcinoma, oesophageal carcinoma, pancreatic carcinoma, gastrointestinal stromal tumour (GIST), neuroendocrine tumours, lung carcinoma, breast carcinoma, ovarian carcinoma, endometrial carcinoma, cervical carcinoma, renal cell carcinoma, transitional cell carcinoma, testicular carcinoma and sarcoma[20].

On ultrasound, most liver metastases appear hypoechoic compared with adjacent liver and hypoechoic haloes (target sign) may be present. Metastases from colonic carcinoma may show calcification, and these may appear echogenic. Other metastases may have a cystic appearance (such as from ovarian carcinoma or pancreatic carcinoma) or central necrosis (such as from cervical carcinoma or rectal carcinoma), reflecting the nature of the primary tumour. On CT, most metastases appear hypodense compared with liver, unless there is fatty liver, in which case the attenuation of liver metastases may be higher than fatty liver parenchyma. Most liver metastases enhance less than the liver on the portal venous phase and may show central contrast washout in the delayed phase. Neuroendocrine tumours and hypervascular liver metastases (such as from renal cell carcinoma and thyroid carcinoma) may show avid arterial phase contrast enhancement[17] and become isodense with the liver on the portal venous and the delayed phases. On MRI, most liver metastases are T1 hypointense, T2 hyperintense and show similar contrast enhancement patterns as in CT. The lesions may show restriction on diffusion weighted imaging. On PET-CT imaging, most liver metastases would appear hypermetabolic to F18-FDG. A few notable exceptions include liver metastases from bronchioloalveolar carcinoma of the lung, gastric carcinoma, well differentiated hepatocellular carcinoma and prostatic carcinoma. The main benefit of PET-CT in imaging liver metastases is that it allows comprehensive whole body staging of the disease.

CONCLUSION

Despite advances in medical imaging, considerable overlap exists between imaging features of benign and malignant liver nodules. Clues from the clinical history and patient presentation remain crucial to the accurate diagnosis of benign and malignant liver nodules, and good communication between radiologists and clinicians is critical. When clinical doubt exists after initial imaging, likely benign lesions can usually be followed up with imaging, while in cases where clinical suspicion of malignancy is high, imaging guided biopsy or thermal ablation can be considered for further management of the patient.

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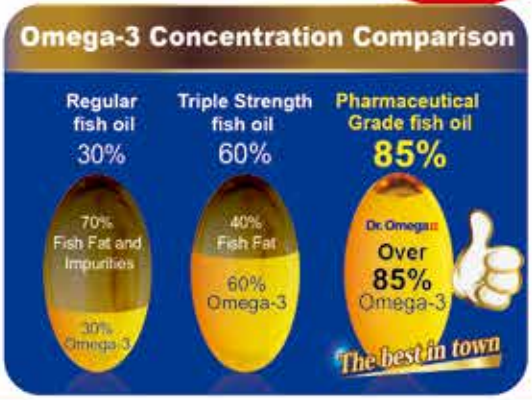

Surgical Management of Early-stage Hepatocellular Carcinoma

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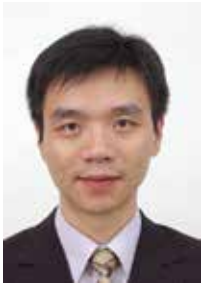

Dr Kelvin KC NG

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy, with a global incidence of more than 84,000 cases annually[1]. It is the sixth most common cancer and the fourth most common cause of cancer-related death worldwide. Current guidelines (Barcelona Clinic Liver Cancer BCLC[2], American Association for the Study of Liver Diseases AASLD[3], European Society for Medical Oncology ESMO[4], and Hong Kong Consensus Statement on the management of HCC[5]) recommend surgical resection, local ablation and liver transplantation as curative treatment options for early-stage HCC. The early-stage HCC refers to tumour size < 2 cm (very early stage) or < 3cm and/or tumour number < 3 (early stage), and with preserved liver function. In general, surgical treatment for HCC can achieve a satisfactory 5-year survival of over 70 % in appropriately selected cases. The location and extent of the tumour, and the status of non-malignant liver tissue must be considered in the choice of surgical procedure. This article summarises the current evidence of surgical management for early-stage HCC.

SURGICAL RESECTION

Surgical resection (hepatectomy) represents the main curative treatment option for patients with HCC in most centres. Ideal candidates for surgical resection are those with early-stage HCC and preserved liver function. Studies have shown the safety of surgical resection with < 2 % perioperative mortality[6, 7]. However, surgical resection in patients with cirrhotic liver carries an increased risk of postoperative liver failure and death. Llovet et al[7]. have shown on an intention-to-treat basis that proper patient selection for the surgical resection of HCC resulted in comparable outcomes to that of liver transplantation. The 1-, 3-, and 5-year survival rates were 85 %, 62 %, and 51 % for surgical resection, which were compared to that for transplantation (84 %, 69 %, and 69 %). Generally speaking, the Child-Pugh classification, which includes bilirubin, albumin, prothrombin time, presence of ascites, and presence of encephalopathy, had been traditionally utilised to select appropriate surgical candidates. While major hepatectomy (resection of > three Cauinaud's segments) is acceptable in patients with Child-Pugh class A, only minor hepatectomy (resection of < three Cauinaud's segments) is allowed in patients with Child-Pugh class B. More recently, the Model for End-Stage Liver Disease (MELD) score has increasingly been shown to predict post-hepatectomy outcomes. Studies have revealed that a cut-off value of MELD score (< 10) was associated with an acceptable surgical risk of morbidity, mortality, and postoperative liver failure[8, 9]. Following resection, portal hypertension and bilirubin are independent prognostic factors. The 5-year survival rate of patients with clinically significant portal hypertension (hepatic venous pressure gradient (HVPG) > 10 mmHg) and bilirubin >1 mg/dl was only 25 %, compared to 74 % 5-year survival rate in patients without portal hypertension and with normal bilirubin levels[7]. Besides scoring systems, more sophisticated methods of measuring portal hypertension, such as indocyanine green retention rate at 15 min < 20 % or HVPG <10 mmHg, can help to select appropriate patients for surgical resection.

In addition to liver function, future liver remnant (FLR), which is a measurement of liver volume remaining after resection, is an important parameter for selecting patients undergoing major hepatectomy. To perform a safe major hepatectomy, Kubota et al.[10] identified that a CT scan could be utilised to adequately determine liver volumetrics. Currently, CT and MRI volumetrics are used to assess liver volume and FLR. It has been recognised that individuals with normal liver function can safely tolerate resection of up to 70 % of normal liver parenchyma, i.e. future liver remnant of 30 % of standard liver mass. As a general rule, hepatic resection is generally considered safe, with a minimal remnant of 30 % in patients with normal liver, and 40 % in select patients with compensated cirrhosis. In case of insufficient future liver remnants, portal vein embolisation (PVE) or associated liver partition with portal vein ligation and staged hepatectomy (ALPPS) can be utilised to induce hypertrophy of the remnant liver. The advantage of ALPPS is the rapid rate of hypertrophy of liver remnant (7 - 14 days), compared with that of PVE (4 weeks to 6 weeks). From a systemic review of the application of ALPPS for HCC, the average median increase in future liver volume was 178 mL, and the average interval between the two stages was 11.2 days[11].

Tumour size and number are important prognostic factors. Surgical resection is a good treatment option in patients with unilobar HCC (< 5 cm) without vascular involvement. With increasing size, poor prognostic factors will be associated with tumours, including vascular invasion (microvascular or macrovascular invasion) and advanced histologic grade. Hence, the chance of sequent tumour dissemination (intrahepatic or extrahepatic metastasis) will be high. As Pawlik et al.[12] demonstrated, the incidence of microscopic vascular invasion increased with tumour size (3 cm, 25 %; 3.1 - 5 cm, 40 %; 5.1 - 6.5 cm, 55 %; > 6.5 cm, 63 %). Surprisingly,

for HCC < 2 cm, there was 27 % chance of microvascular invasion. Besides, patients with multinodular HCC generally experience poor perioperative and long-term outcomes, with 5-year survival as low as 29.9 % compared to 58.4 % in those with a solitary HCC[12, 13]. However, the study has revealed that 5-year survival was > 50 % in patients undergoing resection for multinodular HCC (up to 3 nodules 3 cm) not otherwise suitable for transplantation[14]. While transplantation is considered the standard of care for these patients, there was a 20 % drop-out rate due to progression of the disease. Therefore, select patients with multinodular HCC may benefit from surgical resection.

Ideally, for surgical resection of HCC, anatomic resection should be performed. The tumour is resected together with the tributary of the portal system. In this case, the potential tumour cells seeding within the same portal system as the main tumour can be eliminated to prevent a future intrahepatic recurrence. From an oncologic perspective, anatomic resection is sound because of the high possibility of vascular invasion of segmental portal venous branches by HCC tumour cells. The use of intraoperative ultrasound (IOUS) is important to guide anatomical resection. As revealed in several studies, anatomic resection with adequate surgical margins results in improved survival compared to non-anatomic resection[15]. Anatomical resection was associated with better 1-year (HR 0.79), 3-year (HR 0.87) and 5-year (HR 0.87) disease-free survival than non-anatomical resection.

While survival can reach up to 70 % with surgical resection, it is limited by recurrence in the range of 50 - 70 % at 5 years. For very early HCC (< 2 cm) without microvascular invasion, it is estimated that the 5-year recurrence rate is as high as 50 - 60 %. About 80 % of recurrences are intrahepatic; unfortunately, only 15 % are amenable to repeat resection. Moreover, there is a bimodal distribution of intrahepatic recurrence, with the first peak occurring around one year after resection (early intrahepatic recurrence) and the second peak occurring 4 - 5 years after surgery (late intrahepatic recurrence). It is generally believed that the early intrahepatic recurrence is related to intrahepatic metastasis from the main tumour. Intrahepatic recurrence is related to poor prognostic factors, including non-anatomic resection, microvascular invasion, moderately to the poorly differentiated tumour, number of tumour nodules, satellite lesions, and high AFP level. Meanwhile, late intrahepatic recurrence is more related to 'de novo' tumours and is associated with the stage of liver fibrosis and the grade of hepatitis.

LOCAL ABLATION

Radiofrequency ablation (RFA) produces frictional heat by applying high-frequency alternating current around an active electrode to tissues, with grounding pads to close the electric circuit[16]. The high temperature generated boils, vaporises, necroses, and chars the tissue[17]. The eschar has the unintended consequence of increasing tissue impedance, which limits energy transmission to adjacent cells, thus reducing RFA efficacy towards the peripheries of the ablation zone. Another limitation of RFA is the heat-sink effect that may lead to incomplete ablation for perivascular tumours due to convection cooling into large vessels[18, 19]. For tumours close to bile ducts, RFA might cause biliary complications such as biliary stenosis and biloma.

Microwave ablation (MWA) uses electromagnetic energy around the antenna to deliver thermal energy-induced cellular injury without needing grounding pads. MWA takes a shorter time to reach a threshold temperature, achieves larger and more uniform ablation zones, results in better-delineated ablation zone borders, and is less prone to heat-sink effects from adjacent vascular structures[20]. The size of the ablation zone, however, is harder to predict in MWA compared to RFA[21]. A systematic review of 34 studies, including 12,158 HCC patients treated with PEI, RFA, and MWA reported similar mortality and complication rates among the three techniques, with an overall mortality rate of 0.16 % and a major complication rate of 3.29 %[22]. Complications of these ablative therapies include pain, bleeding, infection, abscess, visceral organ injury, bile leak, liver failure, portal vein thrombosis, cardiac arrhythmias, and pneumothorax[23]. Tumour seeding is observed in 0.5 - 3 % of RFA[24] and MWA[25] procedures, and the risk of tumour seeding can be reduced by cauterisation of the needle trajectory upon withdrawal of the needle and by avoiding direct puncture of subcapsular lesions[23]. Ablation to subcapsular tumours close to neighbouring hollow viscera can result in bowel perforation due to thermal injury to the bowel wall, and such complications can be avoided by the infusion of artificial ascites[26].

RFA is the most used technique for local ablation, with complete response achieved in 70 - 90 % of cases after one or two sessions. Cohort studies have shown that initial complete response was independently and significantly ($p = 0.006$) associated with improved overall survival[27]. The overall survival after RFA ranges from 40 - 68 % at five years and 27 - 32 % at ten years[28 - 31], with the median overall survival of 60 months[32]. The main predictor of RFA treatment failure is tumour size, with better response observed in tumours ≤ 2 cm and reduced response in tumours larger than 2 cm[27, 33 - 35].

Several randomised controlled trials (RCTs) have demonstrated similar survival rates compared to surgical resection in selected patients[36 - 39]. A meta-analysis of 4 RCTs, including 574 patients comparing surgical resection with RFA in early HCC showed no statistical difference in all-cause mortality, although cancer-related mortality and recurrence were lower in the surgery group, while the RFA group had shorter hospital stay and lower adverse event rates[40]. An RCT comparing surgical resection with RFA in 240 patients with recurrent HCC after R0 resection showed o statistical difference in overall survival or disease-free survival. Subgroup analyses showed that surgery was associated with better overall survival in HCCs larger than 3 cm and alpha-fetoprotein (AFP) levels greater than 200 ng/ml but significantly higher complication rates[39]. Given the available evidence, the guidelines have adopted RFA as the front-line treatment for single tumours < 2 cm.

Despite the theoretical advantage of MWA over RFA in its ability to achieve higher ablative temperatures faster and being less subject to the heat-sink effect, several RCTs reported no difference between the two techniques in

local tumour progression, treatment-related morbidity, overall and disease-free survivals[41 - 43]. Similarly, three meta-analyses comparing the two techniques showed similar efficacy, with a trend towards greater efficacy but a higher complication rate in tumours > 3 cm treated with MWA compared with treatment with RFA[44 - 46]. Despite the lack of available evidence to suggest the superiority of MWA over RFA, MWA is widely used in clinical practice.

LIVE TRANSPLANT

Liver transplantation is an attractive treatment option that offers a chance of curing both tumour and underlying cirrhosis. It has gained much enthusiasm worldwide in recent decades, with many clinical advancements. With careful patient selection based on tumour size and number, favourable survival outcomes can be obtained after liver transplantation for HCC using the two widely adopted international selection criteria, namely Milan criteria[47], and the University College of San Francisco (UCSF) criteria[48]. The mismatch between organ donation and the high incidence of HCC mandates a strict and fair system of organ allocation. Before 2009, the priority of patients with HCC on the waiting list is primarily determined by the MELD score. Very often, these patients had low MELD scores at the time of diagnosis of HCC despite the fatal nature of this malignancy. A high drop-out rate (up to 32 %) occurred because of prolonged waiting time and the resulting tumour progression beyond the transplant criteria. To equalise the benefit of transplant to patients with early stage HCC (Stage 2 disease according to the American Liver Tumour Study Group modified tumour-node-metastasis (TNM) staging classification), MELD exception policy was adopted in Hong Kong. This MELD exception policy was proven beneficial in patients with stage 2 HCC, with 80 % 5-year overall survival rate[49].

A significant drop-out rate from the waiting list because of tumour progression has greatly reduced the overall survival of HCC patients waiting for transplantation. It is recommended to adopt local ablation techniques and transarterial chemoembolisation as bridging therapies to halt or delay tumour progression while patients are on the transplant waiting list, with the current enthusiasm for stereotactic body radiation therapy (SBRT) for liver tumours, its efficacy as bridging therapy before transplant is under investigation.

It is plausible in HCC patients with a well-preserved liver function that primary hepatectomy can be safely performed, and salvage transplantation is reserved for recurrence or hepatic decompensation after the initial operation. This approach would certainly reduce the number of HCC patients recruited into the waiting list since those HCC patients are rendered tumour-free after hepatectomy, and there is a time lag between primary hepatectomy and tumour recurrence or liver decompensation. The debate on the choice of primary transplantation versus primary hepatectomy followed by salvage transplantation continues. A recent propensity score matching analysis shows that upfront curative treatment with salvage transplant may result in a higher tumour recurrence rate than primary transplant.[50] Nonetheless, the critical problem of organ shortage in Hong Kong favours the option of primary hepatectomy followed by salvage transplantation. In other words, the pressure on the waiting list would inevitably be reduced by this strategy

Living donor liver transplant (LDLT) can theoretically provide an unlimited source of liver grafts for HCC patients whose tumour status is within the selection criteria. The uncertainty of prolonged waiting time on the list and the risk of drop-out can virtually be eliminated by LDLT. Two decision analyses have supported the application of LDLT for HCC[51, 52]. The unaffected donor pool of organs for patients with non-malignant liver disease is another crucial advantage of LDLT since the living donor graft is a dedicated gift directed exclusively to the recipient. The role of LDLT and its intention-to-treat survival benefit over DDLT in patients with early HCC has been demonstrated. In the former study, a propensity score matching analysis showed that LDLT could achieve recurrence-free survival like DDLT[53]. Nonetheless, the two approaches (LDLT and DDLT) should be considered as complimentary rather than mutually exclusive. The ultimate success of liver transplant for HCC depends on the ability to predict and prevent tumour recurrence after transplant.

Extending the tumour selection criteria to include patients with more advanced HCC to receive LDLT is another issue since a living donor graft is not subject to the system of equitable allocation. It is generally acceptable to have extended criteria for patients with HCC (unlimited tumour size and number) for LDLT, if there is no evidence of major vascular tumour invasion and distant metastasis. Expected inferior post-transplant survival outcomes should be carefully discussed with both donor and recipient. One retrospective study showed that 5-year recurrence-free survival was 62.6 % after LDLT in patients with HCC outside Milan criteria[54].

CONCLUSION

Surgical resection, local ablation and liver transplant are acceptable curative treatment options for early-staged HCC. These treatment options are complimentary to each other, and mutually exclusive. Surgical resection is generally indicated in unilobar tumours with preserved liver function. In the case of bilobar multiple tumours, local ablation is indicated. If patients have HCC with decompensated liver function, a liver transplant is the ultimate goal. By adopting a multidisciplinary approach, liver surgeons, transplant surgeons, hepatologists, interventional radiologists, and clinical oncologists can have detailed discussions to reach sindividualised treatment options.

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Novel First-line Systemic Treatments and New Insights in the Management of Hepatocellular Carcinoma

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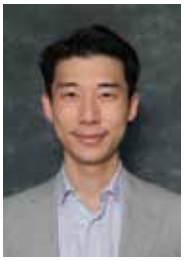

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common cancer and 3rd most lethal cancer in Hong Kong[1]. Aetiology for HCC includes chronic viral hepatitis B/C and metabolic dysfunction-associated steatotic liver disease (MASLD)[2]. In Hong Kong, over 80 % of HCC is due to chronic hepatitis B infection, but the proportion of MASLD-related HCC is expected to increase in future[3]. The prognosis of HCC is generally poor, with a 5-year survival rate of 10 to 20 %[4]. Surgery, transplantation or locoregional therapy is reserved for HCC confined to the liver. However, systemic therapy is indicated in the case of advanced disease or failure/recurrence of previous surgery/locoregional therapy.

It has been estimated that up to 60 % of patients with HCC will receive systemic treatments in their lifespan[2]. For a long time, the search for effective systemic treatment has been slow. Sorafenib, being the first targeted therapy approved for unresectable HCC has been the first approved agent for HCC since 2007, based on phase III clinical trials showing survival benefits as compared to placebo[5, 6]. Lenvatinib is the second drug that was approved in 2018 for HCC based on another phase III clinical trial demonstrating non-inferior survival compared to Sorafenib[7]. Over the past five years, remarkable progress has been made on immunotherapy[8], and second-line multi-targeted kinase inhibitors (MKIs)[9-11]. In particular, the introduction of atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) in 2020 has revolutionised the treatment landscape for HCC as it represented the first systemic treatment that was shown to be superior to Sorafenib[12, 13]. Since then, a plethora of phase III trials have reported improved survival with immunotherapy-based combination therapy[14-16]. Furthermore, emerging evidence has shown that combining locoregional therapy and immunotherapy might be an effective therapeutic strategy for a proportion of patients with advanced HCC[17-20].

In this Review, we will summarise the latest evidence on the novel immunotherapy-based combination systemic treatments and the emerging evidence of combination treatment with locoregional therapy and immunotherapy in HCC.

SCIENTIFIC RATIONALE FOR IMMUNOTHERAPY-BASED COMBINATION THERAPY

Cancer develops and progresses due to evasion from effective immunosurveillance[21]. An effective immunosurveillance is a multistep process which involves the release of cancer cell antigens, cancer antigen presentation, priming and activation of immune cells, trafficking of immune cells to the tumour, infiltration of T-cells through the stroma, recognition of tumour cells by T cells and effective killing of cancer cells (Fig. 1)[21]. It is important to understand that these steps are linked in a cycle, and any malfunctions of individual parts can be the rate limiting step for generating optimal anti-cancer tumour response.

In the past decade, immune checkpoint inhibitors (ICIs) have emerged as a core pillar of cancer treatment in solid malignancies, with indications expanded across multiple cancer types and at different settings[22]. At the moment, three immune-checkpoints have been targeted and used in the clinic, namely PD-L1/PD-1, CTLA-4, and Lag-3[21]. ICIs targeting these checkpoints act at either the priming or effector phase of the cancer-immunity cycle, restoring effective immunosurveillance[23]. Although remarkable response and long-term survivors were observed in certain populations treated with ICIs, it has been estimated that only 15 % of patients who were eligible for ICIs displayed an effective anti-cancer immune response[24]. In other words, the majority of patients had either primary or acquired resistance to ICIs, which could at least be partially explained by the malfunction of the cancer-immunity cycle at multiple points[25]. Therefore, combination therapies targeting different steps in the cancer-immunity cycle have been explored to improve the efficacy of ICIs.

One approach is to target the angiogenesis pathway, especially for hypervascular tumours like HCC. Angiogenesis is a key player in cancer immune evasion. The neovasculatures that support tumour growth are often tortuous and leaky. Inhibitors of angiogenesis, such as the use of vascular endothelial growth factor (VEGF) inhibitors, can normalise the vasculatures to promote effective infiltration of T cells and drugs into the tumour[26]. In addition, pro-angiogenic factors are potent immunosuppressants

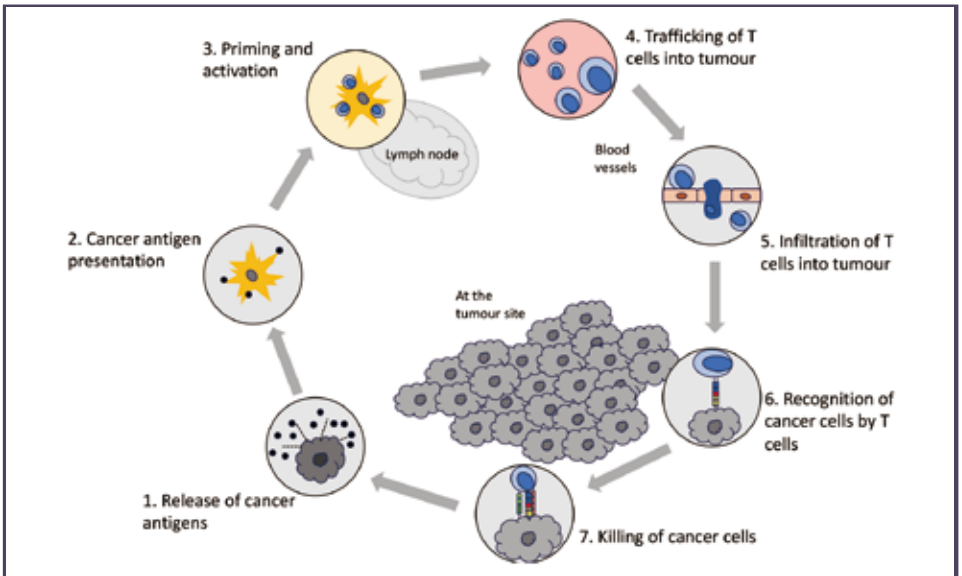

Fig. 1: The cancer-immunity cycle. (Developed by author)

within the tumour microenvironment. Within the tumour microenvironment, the presence of VEGF increases tumour infiltration of immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells, promotes T-cell exhaustion via up-regulation of immune checkpoints, and directly inhibits T-cell proliferation and cytotoxic activities[27]. Therefore, combining anti-VEGF with immunotherapy has been an approach tested in the clinic across multiple cancer types, including HCC[12, 13, 15].

Another approach to reinvigorate the immune system is to expose the tumour neoantigens to the immune system. We now understand that the tumour microenvironments not only consist of tumour cells, but are also supported by other cell types and cytokines[21]. The amalgamation of these cells and molecules together forms a densely packed network of matrix fibres, otherwise known as the tumour stroma. The tumour stroma limits T-cells to infiltrate into the tumour and their ability to respond effectively to checkpoint blockade. Locoregional therapies can disrupt the stroma and expose the tumour antigens to the immune system[28], enabling de-novo immune priming and thus potentiating the anti-tumour response of immunotherapy.

CLINICAL EVIDENCE ON IMMUNOTHERAPY-BASED COMBINATION IN UNRESECTABLE HCC

Single agent immunotherapy showed promises in phase I/II studies in unresectable HCC, with durable response seen in the 15 to 20 % range and exhibiting similar side-effect profiles[8, 14, 29]. However, single ICIs did not meet their study endpoints in their respective phase III trials[30, 31], which led to the pursuit of combination immunotherapy in the hope to improve response and survival based on the promises that they held in preclinical studies and earlier phase studies[32, 33].

Atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) was the first regimen since the approval of Sorafenib in 2007 that demonstrated superior OS in HCC[12, 13]. The IMbrave150 study was a global, randomised, phase III trial that evaluated the combination of atezolizumab plus bevacizumab with Sorafenib in patients with unresectable HCC (Table 1). The study demonstrated improvement in median progression-free survival (PFS) from 4.3 to 6.9 months, and median OS from 13.4 to 19.2 months. The objective response rates (ORR) were unprecedently high at 30 % for patients treated with atezolizumab plus bevacizumab, compared to 11 % only for the sorafenib group. There were no long-term safety concerns at longer follow-up[13]. Importantly, patients were required to have an upper endoscopy screening for varices within six months prior to treatment due to concerns of bleeding with a high dose of bevacizumab.

Since the publication of IMbrave150, results of several similar trials exploring anti-PD-1/L1 plus anti-VEGF agents have been announced. The CARES-310 study was an international, randomised controlled phase 3 trial comparing camrelizumab (anti-PD1) plus anti-VEGFR2 tyrosine kinase inhibitor rivoceranib, vs Sorafenib[15]. Both primary endpoints, the median PFS (5.6 vs 3.7 months) and OS (22.1 vs 15.2 months) were significantly improved with combination therapy. ORR was also significantly improved with camrelizumab plus rivoceranib (25 % vs 6 %). In another study, ORIENT-32, which was a randomised phase 2/3 study conducted in China comparing sintilimab (anti-PD1) plus a bevacizumab biosimilar (IBI305) (anti-VEGF) and Sorafenib, showed that combination therapy was again superior to Sorafenib alone with improved median PFS (4.6 vs 2.8 months), OS (not reached vs 10.4 months) and ORR (21 % vs 4 %)[16].

Another immunotherapy-based combination strategysupported by clinical evidence is the combination of anti-CTLA-4 and anti-PD1 agents,

targeting both the priming and effector phases of the cancer-immunity cycle. Successes have been seen in notably melanoma and renal cell carcinoma[34]. Recently, this approach has also been successfully tested in HCC. The HIMALAYA trial was a global open-label phase III randomised study evaluating the combination of single high-dose tremelimumab (anti-CTLA4) plus durvalumab (anti-PD-L1) vs Sorafenib. The HIMALAYA study met its primary endpoint, with improvement in OS compared to Sorafenib (median OS 16.4 months vs. 13.8 months). Median PFS was not significantly different between the two arms (median 3.8 vs. 4.1 months). Yet, the combination therapy resulted in a higher ORR of 20.1 % compared to 5.1 % for the sorafenib group. Moreover, after longer follow-up at four years, survival benefit was still observed in the group of patients treated with tremelimumab plus durvalumab, with 25 % of patients surviving at four years, compared to only 15.1 % in the sorafenib group[35].

It is important to note that immunotherapy-based combinations may come with a different spectrum of toxicity (Table 1). The most common toxicities associated with anti-VEGF treatment are hypertension and proteinuria. These toxicities are often asymptomatic and can be managed with medications or suspension of treatment. On the other hand, patients with severe portal hypertension are at increased risk of variceal bleeding[36]. In the latest Baveno VII consensus, surveillance with endoscopy and prophylactic treatment with beta-blockers are advocated in this group of patients[37]. It is, therefore, of utmost importance to perform upper endoscopy before starting anti-VEGF treatment, as up to 10 % of patients can develop variceal bleeding with the use of bevacizumab. With this approach, gastrointestinal bleeding was observed in 7 % of patients treated with atezolizumab plus bevacizumab in the IMbrave150 study, and portal-hypertension related acute variceal bleeding was only seen in 2.4 %[38, 39].

The addition of anti-CTLA-4 may also increase the risk of immune-related adverse events[40]. In the HIMALAYA trial, both immune-mediated adverse events requiring high-dose steroids (20.1 % vs 9.5 %), and higher grade immune-mediated adverse events (12.5 % vs. 6.4 %) doubled in the tremelimumab plus durvalumab arm, as compared to single agent durvalumab. The most common grade 3 or higher toxicities in patients treated with tremelimumab plus durvalumab were increased hepatic enzymes, increased lipase, diarrhoea and hyponatremia. In contrast to anti-VEGF agents, given the known mechanism of action of this combination regimen (anti-CTLA-4 and anti-PD-L1), there is no significant increased bleeding risk[14].

In addition, portal vein tumour thrombosis represents one of the most common complications of HCC, and is present in 10 to 40 % of patients at diagnosis[41]. Unfortunately, patients with main portal vein thrombosis were not included in most pivotal clinical trials,except IMbrave150, CARES-310 and ORIENT-32, mainly due to their association with a poor prognosis. Therefore, at the moment, atezolizumab plus bevacizumab is the only regimen registered in Hong Kong suitable for this group of patients. Indeed, a recent exploratory analysis of the IMbrave150 study focusing on the patient population with main portal vein tumour thrombosis showed that a similar magnitude of benefit of atezolizumab plus bevacizumab was seen as compared to the intention-to-treat population[42].

NOVEL COMBINATION STRATEGY WITH LOCOREGIONAL THERAPY AND IMMUNOTHERAPY

Locoregional therapy has a long history in HCC due to the intrinsic multifocal behaviour of HCC. Multiple interventions are considered as locoregional therapy, including radiofrequency ablation (RFA), stereotactic body radiotherapy (SBRT), selective internal radiation therapy (SIRT), transarterial (chemo)embolisation (TAE/TACE). The combination of locoregional therapy with MKIs has been studied extensively before the era of immunotherapy, but none of the prospective trials were positive[43]. Although the RTOG-1112 (Sorafenib plus SBRT vs Sorafenib) and the LAUNCH trial (lenvatinib plus TACE vs lenvatinib) both reported positive readouts recently[44, 45], the RTOG-1112 trial were criticised for the long recruitment period and the use of out-of-favour Sorafenib, and the LAUNCH trial was criticised for the marked inferior performance of the lenvatinib control arm. These have put a halt on the enthusiasm to develop combination strategies of locoregional therapies and systemic treatments.

The introduction and success of immunotherapy in the treatment of HCC have revived the interest in combining locoregional therapy with systemic in the management of HCC. The prospect that this approach holds is that exposing cancer antigens with locoregional treatments to reinvigorate effective immunosurveillance is attractive. Although there is not yet a published randomised phase III trial showing effectiveness of combining locoregional treatment with immunotherapy in HCC, emerging clinical evidence from early phase or retrospective studies supports further investigations with this combination approach, as they have demonstrated promising survival and safety data (Table 2).

Indeed, the EMERALD-1 study has recently announced that it has met its primary endpoint in median PFS[17]. The EMERALD study was phase III randomised controlled, double-blind three-arm study that compared TACE vs TACE plus durvalumab vs TACE plus durvalumab and bevacizumab, in patients with locoregional HCC. As it is the first phase III trial that announced positive readout in the therapeutic strategy of combining locoregional treatment with immunotherapy for HCC, it could potentially be practice changing, and the details of the trial are eagerly awaited in early 2024 when it will be announced at the ASCO Gastrointestinal Cancers Symposium 2024.

CONCLUSION

HCC remains a deadly disease, but survival has improved remarkably in the recent five years due to the introduction of immunotherapy. Advancement in understanding the cancer-immunity cycle has resulted in multiple trials examining immunotherapy-based combination therapy. The results of these trials are largely positive and have already replaced TKIs as the standard first-line treatment in Hong Kong. However,

the toxicities associated with combination therapies require special precautions, especially in those patients who are at high risk of variceal bleeding or with main portal vein tumour thrombosis. Locoregional therapy in combination with immunotherapy has shown promising outcomes, and phase III trials readouts are eagerly awaited in the future.

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Table 1. Key Phase III trials examining immunotherapy-based combination for unresectable HCC. (Developed by author)

Study name (year)	n	Aetiology, %			EHD, %	BCLC C, %	MVI, %	mPFS, months	mOS, months	ORR, %	TRAE grade 3-4, %	TRAE leading to discontinuation of any drug, %
		HBV	HCV	Non-viral								
IMbrave150 (2020) [12, 13]												
Atezolizumab plus bevacizumab	336	49	21	30	63	85	38	6.9	19.2	30	43	22
Sorafenib	165	46	22	32	56	84	43	4.3	13.4	11	46	12
ORIENT-32 (2021) [16]												
Sintilimab plus bevacizumab biosimilar	380	94	2	4	73	85	28	4.6	NR	21	34	14
Sorafenib	191	94	4	2	75	86	26	2.8	10.5	4	36	6
HIMALAYA (2022) [14]												
Durvalumab plus tremelimumab	393	31	28	41	53	80	26.2	3.8	16.4	20	50.5	14
Sorafenib	389	30	27	43	52	80	25.7	4.1	13.7	5	52.4	17
COSMIC-312 (2022)[46]												
Atezolizumab plus cabozantinib	432	29	31	39	54	68	31	6.8	15.4	11	54	14
Sorafenib	217	29	31	40	56	67	28	4.2	15.5	4	32	8
CARES-310 (2023)[15]												
Camrelizumab plus rivoceranib	272	76	8	15	64	86	15	5.6	22.1	25	81	24
Sorafenib	271	73	11	17	66	85	19	3.7	15.2	6	52	4
LEAP-002 (2023)[47]												
Pembrolizumab plus lenvatinib	395	49	24	30	63	78	18	8.2	21.2	26.1	63	18
Lenvatinib	399	49	22	33	61	76	16	8.0	19.0	17.5	58	11

BCLC, Barcelona Clinic Liver Cancer; EHD, extrahepatic disease; mPFS, median progression-free survival; mOS, median overall survival; MVI, macrovascular invasion; ORR, overall response rate; TRAE, treatment-related adverse event

Table 2. Selected early phase prospective trials examining combination of locoregional treatment with immunotherapy in HCC. (Developed by author)

Locoregional treatment	Immunotherapy	n	BCLC-B/C, %	ORR (RECIST 1.1), %	Median OS, months	Treatment related deaths, %	Ref
SIRT	Nivolumab	42	74/26	41.5	20.9	0	De la Torre 2022[48]
SIRT	Nivolumab	36	33/67	30.6	16.9	0	Tai 2021[49]
SBRT	Nivolumab	30	13/40	17	Not reached; 3-year OS: 63.9%	0	Chiang 2023[50]
SBRT, TACE	Avelumab	33	24/64	24	30.3	0	Chiang 2023[18]

BCLC, Barcelona Clinic Liver Cancer; ORR, overall response rate; OS, overall survival; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation

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9 May 2024	Patient Complaints	Dr. Ludwig TSOI 蔡振興醫生 Specialist in Emergency Medicine
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	Common Molecular Cytogenetic Tests	Dr. Sandy AU Scientific Officer (Med) Prenatal Diagnostic & Counselling Division Department of Obstetrics and Gynaecology Tsan Yuk Hospital
14 May 2024	Low-Pass Whole Genome Sequencing for Germline Copy Number Variants	Dr. Timothy CHENG Consultant Department of Pathology Hong Kong Children's Hospital
21 May 2024	Blood Cancer Cytogenomics	Dr. Jason SO Chief of Service Department of Pathology Hong Kong Children's Hospital
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4 June 2024	Rings and Things and Fine Array	Dr. Stephanie HO Associate Consultant Clinical Genetics Service Unit Hong Kong Children's Hospital
11 June 2024	Constitutional Cytogenetic Disorders and Genetic Counseling	Dr. Shirley CHENG Consultant Clinical Genetics Service Unit Hong Kong Children's Hospital

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Course Feature : Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors : DOCTORS are required to complete a quiz after the completion of each lecture
Language Media : Cantonese (Supplemented with English)
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Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
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The Global Investment Landscape in 2024

Mr Paul PONG

Managing Director, Private Investment Company

Mr Paul PONG

The global economy will continue navigating uncertainties in 2024 as central banks work to balance inflation reduction and economic growth. Geopolitical tensions and upcoming elections around the world could also fuel market volatility. However, certain sectors and countries may see opportunities emerge.

US MARKET: STILL GROWING, BUT RISKS EMERGE

In the United States, the stock market is positioned for gains despite macroeconomic headwinds. While recession risks remain, earnings growth could drive indices like the S&P 500 higher. Our year-end 2024 target range is 4,900 to 5,100, representing a 3 - 6 % increase from current levels. Technology companies that are leading advances in artificial intelligence should continue delivering strong returns, particularly the "magnificent seven" of Apple, Microsoft, Alphabet, Amazon, Meta, Nvidia and Tesla.

However, investors must watch inflation closely. While the job market and consumer spending have remained resilient even as the Fed hikes rates, price increases could reaccelerate if wage growth outpaces productivity. Housing costs are also an area of concern, as higher mortgage rates have yet to significantly impact home values or rents. Election uncertainty could also roil markets in the lead up to the presidential vote. A divided government may constrain spending. Recession odds within the next year have risen. A downturn would pressure profits and multiples.

ASIA MARKETS: SELECTIVE OPPORTUNITIES EMERGE

Outside the U.S., Japan and India offer compelling long-term opportunities. Japan exited its decades-long deflation cycle in 2023, supporting corporate profits and consumer spending. Structural reforms to promote export, domestic consumption and immigration should further power economic expansion. India, meanwhile, is poised to be one of the fastest growing major economies globally as it leverages favourable demographics and a large domestic market. Both countries stand to benefit from ongoing diversification away from China (de-risking).

While the Hang Seng Index has witnessed four straight years of losses, we believe allocating a portion of a portfolio to Chinese stocks makes sense at this juncture. Valuations across many Chinese and Hong Kong-listed companies appear quite depressed after the prolonged market downturn. Sentiment remains bearish, which means there is potential for positive surprises to the upside if economic conditions stabilize or improve from here. Should the market environment turn, upside potential appears significant versus other major global indices that have already rallied strongly.

Importantly, the outlook could brighten significantly as monetary conditions loosen. There is a reasonable chance rate cuts follow in 2024 if inflation pressures recede enough and signs of a genuine slowdown emerge. Easier financial conditions overseas would alleviate headwinds for the Hong Kong stock market.

ALTERNATIVE STRATEGIES: CRYPTO COMES OF AGE

Another area with upside potential is digital currencies. The Bitcoin will undergo its fourth "halving" in 2024, meaning miners' rewards will drop by half - an event that has historically preceded bull markets. Increased institutional adoption and potentially more favourable regulations, such as the approval of a spot Bitcoin ETF, could drive greater participation and liquidity. While digital assets remain highly volatile, allocating a small portion of a portfolio to Bitcoin may enhance returns through its non-correlation with other holdings. This maturing space demands open-minded consideration within diverse portfolios.

Overall, a balanced, globally diversified portfolio positions investors well for what's shaping up to be an uncertain yet opportunity-rich 2024. The key will be maintaining exposure to areas benefiting from long-term innovation and growth trends while hedging against macroeconomic shifts through effective asset allocation and risk management. Flexibility will also be paramount to navigating unexpected election outcomes and geopolitical developments. With a disciplined, patient approach, savvy investors stand to make progress even in a slower growth environment.

Table 1: Balanced Portfolio (Stock & Bond). (Adapted from reference 1)

Balanced Portfolio (Stock & Bond)			
	2023*	5Y Annualised*	Allocation
MSCI ACWI Index	17.14%	9.61%	30%
S&P Technology Select Sector Index	49.86%	23.66%	20%
CRSP US Large Cap Value Index	3.96%	8.50%	15%
Bloomberg US Aggregate Bond Index	1.64%	0.71%	25%
Markit iBoxx USD Liquid High Yield Index	8.75%	3.55%	10%

**As of 30-11-2023*

Table 2: Growth Portfolio. (Adapted from reference 1)

Growth Portfolio			
	2023*	5Y Annualised*	Allocation
S&P Technology Select Sector Index	49.86%	23.66%	45%
Nikkei 225 Index	28.33%	8.20%	15%
ARK - Innovation ETF	47.60%	1.95%	15%
MSCI India Index (USD)	10.61%	8.83%	15%
MSCI China Index (USD)	-9.00%	-3.54%	10%

**As of 30-11-2023*

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Medical Diary of April

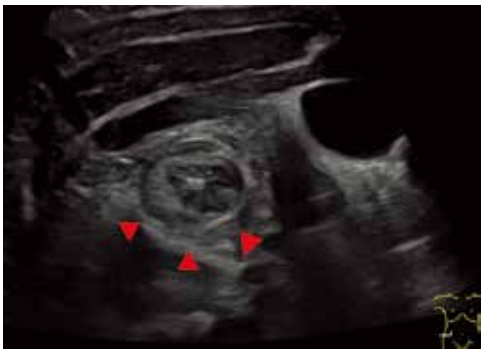
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	★In-person / Zoom HKMA-HKSH CME Programme 2023-2024 Topic: TBC 2	★Certificate Course in Common Urological Problems 2024 (Video Lectures) 3	4	5	6
★FMSHK Sports Day 2024 7	8	9	★The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed ★In-person / Zoom HKMA-CUHK Medical Centre CME Programme 2024 Common Health Problems - Topic: Open vs Endovenous Varicose Vein Surgery ★Certificate Course in Common Urological Problems 2024 (Video Lectures) 10	11	12	13
14	15	★In-person / Zoom HKMA-GHK CME Programme 2024 Topic: TBC 16	★Certificate Course in Common Urological Problems 2024 (Video Lectures) 17	★In-person The HKMA CME Lecture for District Health Network CME Programme Topic: Guarding Against Hidden Threat – The Local Rising Disease ★FMSHK Executive Committee Meeting 18	★Zoom Topic: COVID-19 Vaccine Performance: Interpreting Efficacy, Effectiveness, and Immunogenicity 19	20
21	★Zoom Topic: ROSACEA - Diagnosis and Treatment 22	23	★Certificate Course in Common Urological Problems 2024 (Video Lectures) 24	25	★Zoom Topic: Understandings of Colorectal Polyps and Polyposis Syndromes Advancement in Early Detection and Prevention of Recurrence 26	27
28	29	30				

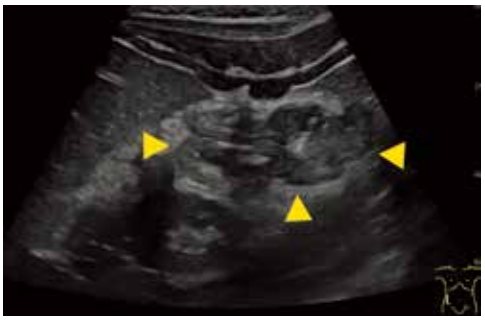
Date / Time	Function	Enquiry / Remarks
2 TUE 2:00 PM	**In-person / Zoom** **HKMA-HKSH CME Programme 2023-2024** **Topic: TBC** Organiser: The Hong Kong Medical Association and Hong Kong Sanatorium & Hospital Speaker: Dr Amy Lee WONG Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
3 WED 7:00 PM	**Certificate Course in Common Urological Problems 2024 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr CHEUNG Man-chiu and Dr Trevor Churk-fai LI	Ms ToTo CHAN Tel: 2527 8898
7 SUN 1:00 - 8:00 PM	**FMSHK Sports Day 2024** Organiser: The Federation of Medical Societies of Hong Kong Venue: Ying Wa College	Ms Lucy LAU Tel: 2527 8898
10 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting - To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker(s): Dr Christopher Hiu-fung SUM Chairman: Dr PO Yin-chung Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital; or via Zoom meeting	CME Accreditation College: 1.5 points College of Surgeons of Hong Kong Enquiry: Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061
2:00 PM	**In-person / Zoom** **HKMA-CUHK Medical Centre CME Programme 2024** **Common Health Problems - Topic: Open vs Endovenous Varicose Vein Surgery** Organiser: The Hong Kong Medical Association and CUHK-Medical Centre Speaker: Dr TONG Wai-chung Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
7:00 PM	**Certificate Course in Common Urological Problems 2024 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Phoebe Man-hung CHEUNG. Dr Raymond Wai-man KAN	Ms ToTo CHAN Tel: 2527 8898
16 TUE 2:00 PM	**In-person / Zoom** **HKMA-GHK CME Programme 2024** **Topic: TBC** Organiser: The Hong Kong Medical Association and Gleneagles Hong Kong Hospital Speaker: To-be-confirmed Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
17 WED 7:00 PM	**Certificate Course in Common Urological Problems 2024 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr MA Wai-kit, Dr Victor Hip-wo YEUNG	HKMA CME Dept. Tel: 2527 8452 1 CME Point
18 THU 8:00 PM	**In-person** **The HKMA CME Lecture for District Health Network CME Programme** **Topic: Guarding Against Hidden Threat – The Local Rising Disease Burden OF HPV-Related OPC** Organiser: The HKMA District Health Network Speaker: Dr Julian Kay-chung YAU Venue: Star Room, Level 42, Cordis Hong Kong, 555 Shanghai Street, Mong Kok, Kowloon, Hong Kong	HKMA DHN Dept. Tel: 3108 2514 1 CME Point
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
19 FRI 2:00 PM	**Zoom** **Topic: COVID-19 Vaccine Performance: Interpreting Efficacy, Effectiveness, and Immunogenicity** Organiser: The Hong Kong Medical Association Speaker: Dr Wilson LAM	HKMA CME Dept. Tel: 2527 8452 1 CME Point
22 MON 2:00 PM	**Zoom** **Topic: ROSACEA - Diagnosis and Treatment** Organiser: The Hong Kong Medical Association Speaker: Dr Johonny Chun-yin CHAN	HKMA CME Dept. 2527 8452 1 CME Point
24 WED 7:00 PM	**Certificate Course in Common Urological Problems 2024 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr FAN Chi-wai, Dr Wayne Pei LAM	Ms ToTo CHAN Tel: 2527 8898
26 FRI 2:00 PM	**Zoom** **Topic: Understandings of Colorectal Polyps and Polyposis Syndromes Advancement in Early Detection and Prevention of Recurrence** Organiser: The Hong Kong Medical Association Speaker: Dr LO Siu-hung	HKMA CME Dept. Tel: 2527 8452 1 CME Point

Answers to Radiology Quiz

Answers:

1. Target sign (figure A - Red arrowheads) and pseudokidney appearance (figure B - Yellow arrowheads) are noted in the ileo-caecal junction.





2. Ileocolic intussusception

3. After ruling out contraindication, e.g. pneumoperitoneum, pneumatic reduction could be performed under intermittent fluoroscopic screening

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Reference:
1. Epclusa Prescribing Information. (Version: HK-APR22-EU-MAR21-ICGPS-AUG20).
2. Solomon SS, Wagner-Cardoso S, Smeaton L, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2022;7(4):307-317.

EPCLUSA® Abbreviated Prescribing Information (Version: HK-APR22-EU-MAR21-ICGPS-AUG20) **Presentation:** Pink, diamond-shaped, film-coated tablet of dimensions 20 mm x 10 mm, debossed on one side with "GSI" and "7916" on the other side. **Indications:** Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older and weighing at least 30 kg. **Dosage:** Adults: one tablet, taken orally, once daily with or without food for 12 weeks. Patients aged 12 to < 18 years and weighing at least 30 kg: one tablet, taken orally, once daily with or without food for 12 weeks. Adult patients who have previously failed therapy with an NS5A-containing regimen: Epclusa with ribavirin for 24 weeks may be considered. Elderly: No dose adjustment is warranted for elderly patients. Renal impairment: Epclusa can be used in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) and end stage renal disease (ESRD) requiring haemodialysis with no dose adjustment. Hepatic impairment: No dose adjustment of Epclusa is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C). Safety and efficacy of Epclusa have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis. Paediatric population: The safety and efficacy of Epclusa in children aged less than 12 years or weighing less than 30 kg have not yet been established. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Medicinal products that are strong P-glycoprotein (P-gp) or strong cytochrome P450 (CYP) inducers (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort). **Warnings and Precautions:** Epclusa should not be administered concurrently with other medicinal products containing sofosbuvir. Severe bradycardia and heart block: Life-threatening cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone. Amiodarone should only be used in patients on Epclusa when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated. Patients should undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Epclusa. All patients with concurrent or recent use of amiodarone should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them. HCV/HBV (hepatitis B virus) co-infection: Cases of HBV reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines. Patients who have previously failed therapy with an NS5A-containing regimen: There are no clinical data to support the efficacy of sofosbuvir/velpatasvir for the treatment of patients who have failed treatment with a regimen containing another NS5A inhibitor. Treatment with Epclusa + RBV for 24 weeks can be considered for patients who have failed therapy on an NS5A-containing regimen and who are deemed at high risk for clinical disease progression and who do not have alternative treatment options. Renal impairment: Safety data are limited in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) and ESRD requiring haemodialysis. Epclusa can be used in these patients with no dose adjustment when no other relevant treatment options are available. Use with moderate P-gp inducers or moderate CYP inducers: Co-administration of such medicinal products that are moderate P-gp or moderate CYP inducers (e.g. efavirenz, modafinil, oxcarbazepine or rifapentine) with Epclusa is not recommended. Use with certain HIV antiretroviral regimens: Patients receiving Epclusa concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Use in diabetic patients: Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated. CPT Class C cirrhosis: Safety and efficacy of Epclusa has not been assessed in patients with CPT Class C cirrhosis. Liver transplant patients: The safety and efficacy of Epclusa in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. **Adverse reactions:** Common adverse drug reactions include rash. Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone and/or other medicinal products that lower heart rate. Steven-Johnson syndrome with unknown frequency. **Drug interactions:** Patients treated with vitamin K antagonists: As liver function may change during treatment with Epclusa, a close monitoring of International Normalised Ratio (INR) values is recommended. Impact of DAA therapy on drugs metabolized by the liver: The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV. Interactions between Epclusa and other medicinal products: Acid reducing agents including antacids (aluminium, magnesium hydroxide, calcium carbonate), H2-receptor antagonists (famotidine, cimetidine, nizatidine, ranitidine), proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole); Antiarrhythmics such as amiodarone, digoxin; Anticoagulants such as dabigatran etexilate and Vitamin K antagonists; Anticonvulsants such as carbamazepine, phenytoin, phenobarbital and oxcarbazepine; Antimycobacterials such as rifampicin, rifabutin and rifapentine; HIV antiviral agents: reverse transcriptase inhibitors such as tenofovir disoproxil fumarate, efavirenz/ emtricitabine/ tenofovir disoproxil fumarate; Herbal supplements such as St. John's wort; HMG-CoA reductase inhibitors such as rosuvastatin, and other statins. Immunosuppressants such as ciclosporin and tacrolimus.

Before prescribing, please consult full prescribing information which is available upon request.

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Important Notice: Breast-feeding is the best form of nutrition for babies and provides many benefits to babies and mothers. It is important that, in preparation for and during breast-feeding,pregnant and lactating women eat a healthy, balanced diet. Combined breast and bottle-feeding in the first weeks of life may reduce the supply of their own breast-milk, and reversing the decision not to breast-feed is difficult. Always consult healthcare professional for advice about feeding baby. If infant formula is used, mothers / care givers should follow manufacturer's instructions for use carefully- failure to follow the instructions may make baby ill. The social and financial implications of using infant formula should be considered. Improper use of an infant formula or inappropriate foods or feeding methods may present a health hazard.

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