(02)

病毒性肝炎、肝癌與門脈高壓：診斷與治療的永續創新

Viral Hepatitis, Liver Cancer, and Portal Hypertension: Sustainable Innovations in Diagnosis and Treatment

時　間：113 年 6 月 22 日(星期六) 08:30~17:25
地　點：臺北榮民總醫院 致德樓第二會議室

08:30-08:35	***Opening Remarks***	侯明志副院長 Ming-Chih Hou
	座長：霍德義 教授 (Teh-Ia Huo)	
08:35-09:05	B 型肝炎在肝癌發生中的角色 The Role of HBV in Hepatocarcinogenesis	葉昭廷教授 Chau-Ting Yeh
	座長：吳肇卿 教授 (JAW-CHING WU)	
09:05-09:35	抗病毒藥物對不典型 B 型肝炎患者治療的利弊 The Cons and Pros of Antiviral Therapy for Patients in the Gray Zone	黃麗虹教授 Lai-Hung Wong 香港中文大學
	座長：朱啟仁 副教授 (Chi-Jen Chu)	
09:35-10:00	慢性 B 型肝炎抗病毒藥物停藥或長期用藥的利弊 Finite Therapy Versus Continuous NUCs Therapy for Patients with Chronic Hepatitis B	許耀峻教授 Yao-Chun Hsu
10:00-10:20	***Coffee Break***	
	座長：林漢傑 教授 (Han-Chieh Lin)	
10:20-11:00	**Keynote Speech (1):** B 型肝炎表面抗原廓清或 C 型肝炎治癒對肝癌的影響 The Risk of HCC After HBsAg Seroclearance or HCV Clearance after Antiviral Therapy	余明隆教授 Ming-Lung Yu
	座長：李發耀 教授 (Fa-Yauh Lee)	
11:00-11:25	白蛋白在病危肝硬化病患的角色 The Role of Albumin in Critically Ill Cirrhotic Patients	蔡銘鴻教授 Ming-Hung Tsai
	座長：許劭榮 副教授 (Shao-Jung Hsu)	
11:25-11:50	精準醫療、多體學及大數據在慢性肝病的應用 Precision Medicine, Multi-Omics, and Big Data in Chronic Liver Diseases	蘇東弘副教授 Tung-Hung Su
11:50-12:30	***Lunch***	

座長：李癸泗 教授 (Kuei-Chuan Lee)

13:15-13:40	酒精性肝病患者的酒癮戒治 Abstinence In Alcoholic Liver Disease	林志文教授 Chih-Wen Lin

座長：羅景全 教授 (Jiing-Chyuan Luo)

13:40-14:05	腸道微菌叢在門脈高壓及肝癌的角色 Microbiota in Portal Hypertension and HCC	李沛璋醫師 Pei-Chang Lee

座長：楊盈盈 教授 (Ying-Ying Yang)

14:05-14:30	肝癌患者門脈高壓之治療 Management of Portal Hypertension in Patients with HCC	陳文誌副教授 Wen-Zhi Chen

座長：黃惠君 教授 (Hui-Chun Huang)

	Keynote speech (2):	
14:30-15:10	營養不良、虛弱及肌少症對門脈高壓及肝癌的影響 Malnutrition, Frailty, and Sarcopenia in Patients with Portal Hypertension and HCC	Prof. Jennifer C. Lai (University of California, San Francisco) 美國
15:10-15:30	***Coffee Break***	

座長：王嘉齊 教授 (Chi-Chi Wang)

15:30-16:00	免疫治療在肝癌之困境 Unmet Needs of Immunotherapy in HCC	許駿教授 Chiun Hsu

座長：李騰裕 副教授 (Teng-Yu Lee)

16:00-16:25	肝癌治癒後再復發的預測及治療 Updates in Prediction and Management of HCC Recurrence after Curative Treatment	李懿宬副教授 I-Cheng Lee

座長：黃怡翔 教授 (Yi-Hsiang Huang)

16:25-16:55	免疫治療在中期肝癌的角色 Refining Treatment Strategies in Intermediate-Stage HCC in the Era of Immunotherapy	Prof. Hideki Iwamoto (Kurume University School of Medicine, Kurume, Japan) 日本

座長：施宇隆 處長 (Yu-Lueng Shih)

16:55-17:20	肝癌的經動脈給藥治療 Intra-Arterial Therapy for HCC	梁博欽主任 Po-Chin Liang
17:20-17:25	***Closing Remarks***	黃怡翔教授 Yi-Hsiang Huang

The role of HBV in hepatocarcinogenesis

B 型肝炎在肝癌發生中的角色

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The role of HBV in oncogenesis of liver cancer has long been supported by epidemiological data, including serological evidence and viral load association. Subsequently, it was found that antiviral therapy significantly reduced liver cancer development and neonatal vaccination program significantly reduced liver cancer occurrence in children. Molecular oncogenesis investigation reveals that HBV-hepatocarcinogenesis can be caused by multiple mechanisms: (i) expression of wild type or mutant viral proteins, including X or X truncation proteins, pre-S2 truncation or S truncation proteins, and large (pre-S1) protein; (ii) integration of HBV genomic DNA into critical chromosomal sites; (iii) host genomic mutations caused by hepatocyte proliferation; (iv) microenvironmental changes including inflammatory cells and immune factor changes, epigenetic changes, and others. Recent studies also suggested contribution roles of lncRNA, miRNA, cccDNA, and microbiota in HBV-hepatocarcinogenesis. Most convincing experimental evidence comes from transgenic mice models, although it is unknown how big the gap is between mice and human in terms of hepatocarcinogenesis. Other experimental approaches include survival correlation and tumor growth promoting effects in cell-based and xenograft models. The latter methods can lead to arguments that the proposed mechanisms are in fact cancer growth-maintaining/promoting factors instead of hepatocarcinogenetic factors. Finally, recent studies suggested that prolonged antiviral treatments without complete suppression of HBV might lead to selection of oncogenic HBx mutants. Further investigation is required to confirm/reject the latter argument.

The cons and pros of antiviral therapy for patients in the gray zone

抗病毒藥物對不典型 B 型肝炎患者治療的利弊

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Chronic hepatitis B virus (HBV) infection is a highly dynamic chronic disease which evolves over decades into different phases, traditionally labelled as immune tolerant phase, immune active phase, and inactive phase. Yet, a significant number of patients with chronic hepatitis B do not align with these well-defined phases, leading to a category known as the gray zone, in which patients do not fulfill the specific criteria for any of the recognised phases. Consequently, under current guidelines, patients in gray zone often do not receive antiviral therapy, presenting unique challenges in their treatment and care. With evolving evidence, key international societies are now in the process of updating their clinical practice guidelines on HBV. The experts around the world are making every effort to improve the management of this complex and dynamic chronic infection which may lead to cirrhosis and its complications, hepatocellular carcinoma (HCC), and hence causing substantial morbidity and mortality. In the last versions of the key international guidelines, treatment indications were defined according to the degrees of viral replication (i.e., serum HBV DNA level) and liver inflammation (i.e., serum alanine aminotransferase [ALT] level). The cutoff value for HBV DNA is often set at 2,000 IU/mL, as patients with such viral load above this cutoff are at increased risk of developing liver cirrhosis and HCC according to the landmark REVEAL study published two decades ago. On the other hand, serum ALT may fluctuate over time and not reflect hepatic necroinflammatory activity reliably, especially in patients with hepatitis B e antigen (HBeAg)-negative CHB, and hence been challenged as a reliable indicator of antiviral therapy. In this lecture, the latest evidence of then natural history and the pros and cons of antiviral therapy on gray zone is discussed.

Finite therapy versus continuous NUCs therapy for patients with chronic hepatitis B

慢性 B 型肝炎抗病毒藥物停藥或長期用藥的利弊

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Chronic hepatitis B (CHB) remains a major threat to public health around the world, including Taiwan. Nucleos(t)ide analogues (NUCs) have been the mainstay of treatment for CHB, effectively suppressing viral replication and reducing the risk of liver-related complications. However, the optimal duration of NUCs therapy remains a topic of debate. This speech aims to discuss the advantages and disadvantages of finite therapy compared to continuous NUCs therapy in patients with CHB.

Current guidelines recommend indefinite NUCs therapy for most CHB patients, as it has been shown to reduce the risk of hepatocellular carcinoma (HCC) and improve overall survival. Despite the benefits of long-term NUCs therapy, seroclearance of hepatitis B surface antigen (HBsAg) rarely occurs with this approach, raising the concerns of various drawbacks of lifelong treatment. In contrast, finite therapy, which involves discontinuing NUCs after a defined period of viral suppression, has been proposed as an alternative approach to induce HBsAg seroclearance.

This speech will review the current evidence from clinical trials and observational studies to examine the rates of sustained viral response, HBsAg loss, and HBeAg seroconversion, as well as the incidence of virological relapse, biochemical flares, and liver-related complications after NUCs discontinuation. The speech will also cover factors that predict different outcomes following NUCs cessation.

In conclusion, the speaker will provide a comprehensive overview of the current evidence and future perspectives on finite therapy versus continuous NUCs therapy for patients with CHB, with the goal to help optimize treatment strategies and improve clinical outcomes for individual patients.

The risk of HCC after HBsAg seroclearance or HCV clearance after antiviral therapy

B 型肝炎表面抗原廓清或 C 型肝炎治癒對肝癌的影響

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Both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are significant global health threats, contributing to the development of hepatocellular carcinoma (HCC), a prevalent human cancer with high mortality. The progression from chronic viral infection to HCC can span several decades and is affected by various factors such as age at infection, viral genotype, comorbidities, environment and liver fibrosis. While universal HBV vaccination has substantially decreased HBV infection rates and HCC incidence, currently, no vaccine exists for HCV. Hence, effective antiviral therapy plays a pivotal role in HCC prevention, encompassing the treatment of chronic HBV infection and achieving sustained virological response (SVR) in HCV infections.

Eradicating HCV through SVR or sustained suppression of HBV replication has been demonstrated to reduce the incidence of HCC and liver-related mortality. Nevertheless, the risk of HCC remains after viral suppression or even viral eradication. Factors like preexisting liver cirrhosis and age are generalized recognized as contributors to HCC risk among individuals with suppressed HBV or achieved HCV SVR. Epigenetic modifications, including alterations in H3K27ac, have been linked to increased expression of oncogenes and decreased tumor suppression genes, further elevating the risk of liver cancer post-SVR.

Several risk factors associated with post-SVR HCC have been identified, including advanced fibrosis, diabetes, alcohol consumption, higher bilirubin levels, persistent high FIB-4 scores, elevated baseline alpha-fetoprotein (AFP) levels, and specific host genetic variations (MICA, PNPLA3, MBOAT7, TM6SF2, and GCKR). Moreover, metformin and statins have exhibited potential chemopreventive effects against HCC development among HCV-cured or HBV-suppressed patients, as indicated by large-scale cohort studies.

In summary, while significant strides have been made in reducing the burden of HCC through HBV vaccination and effective antiviral therapy, challenges persist in preventing HCC among individuals with viral infections. Unraveling the underlying mechanisms and identifying surrogate biomarkers associated with HCC risk in individuals with viral suppression can inform the development of effective follow-up strategies. Continued research efforts and comprehensive approaches are imperative to further mitigate the burden of HCC among individuals with chronic HBV and HCV infections, including surveillance, risk stratification, and targeted interventions for high-risk populations.

The role of albumin in critically ill cirrhotic patients

白蛋白在病危肝硬化病患的角色

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Albumin is synthesized by liver and secreted into circulation. Albumin has multiple biological functions. Albumin contributes to 75-80 % of the plasma oncotic pressure because of its molecular mass and negative charge. Because of these oncotic effects, albumin has been used as a volume expander. In fact, albumin infusion is recommended to prevent or treat some complications of decompensated cirrhosis based on its ability to expand plasma volume, including circulatory dysfunction after large-volume paracentesis, and hepatorenal syndrome. In addition to its effects on oncotic pressure, it may serve as a radical scavenger, antioxidant, and immune modulator.

With the progression of liver cirrhosis, albumin decreases in quantity and quality. In patients with acute decompensation and acute on chronic liver failure, toxic oxidized isoforms of albumin increase significantly. Albumin infusion in such subgroups of patients may be beneficial. However, the optimal dosage and frequency of albumin infusion have not yet been defined. Removal of the dysfunctional and toxic isoforms by albumin dialysis may be helpful in some clinical settings. Further investigations are needed. Albumin therapy is not without adverse effects. Pulmonary edema may develop in cirrhotic patients with limited cardiac reserve especially in the setting of acute and short-term treatment for cirrhotic patients with acute decompensation and acute on chronic liver failure.

Precision medicine, multi-omics, and big data in chronic liver diseases

精準醫療、多體學及大數據在慢性肝病的應用

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Liver diseases present a significant global health challenge, necessitating innovative and comprehensive approaches to understanding and managing these conditions effectively. The convergence of cutting-edge technologies drives a paradigm shift in liver disease research and treatment.

Omics refers to high-throughput technologies such as genomics, proteomics, transcriptomics, and metabolomics, enabling researchers to analyze the complete set of molecules within biological samples. These tools offer invaluable insights into the molecular mechanisms underlying liver diseases, identifying disease-specific biomarkers and therapeutic targets, thus facilitating personalized treatment strategies.

With the digitalization of medical records, electronic medical records become a valuable database for big data research. Through reasonable data management and curation, retrospective cohorts are generated to provide real-world evidence to address questions that clinical trials cannot answer. Insights from medical big data also support the design of prospective studies to validate important ideas.

These novel approaches empower researchers and clinicians to unravel the complexities of liver diseases and develop more effective therapeutic interventions.

Abstinence in alcoholic liver disease

酒精性肝病患者的酒癮戒治

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Alcoholism remains a major cause of liver disease and is a global health problem worldwide. Alcoholic liver disease (ALD) encompasses a spectrum of injury including steatosis, hepatitis, hepatitis on cirrhosis, and cirrhosis. ALD can lead to fibrosis, cirrhosis, HCC, and mortality. Economic progress has led to an increase of alcohol consumption and changes in drinking behavior, which have resulted in an increased number of cases of ALD in Taiwan. Taiwan has a high prevalence of hepatitis B viral (HBV) infection and hepatocellular carcinoma (HCC) with increasing consumption of alcohol. Our previous study demonstrated that heavy alcohol consumption with ALDH2 polymorphism was associated with increased incidence of HCC and mortality in patients with HBV-related cirrhosis and abstinence from alcohol was associated with reduced risk of HCC and mortality in patients with cirrhosis with HBV infection and alcoholism. Abstinence from alcohol is the cornerstone of treatment and should be recommended to all patients with ALD. Abstinence reduces the risk of HCC, hepatic decompensation and death in cirrhosis patients. Multiple treatment modalities are available, including behavioral therapy, peer-led support programs, and pharmacotherapy. In patients with ALD, the combination of comprehensive medical care and psychosocial interventions are more likely to result in abstinence, and integrated care approaches are associated with better outcomes. Recently, acamprosate, disulfiram and naltrexone are approved by the US FDA and European Medicines Agency for use in alcohol use disorder (AUD). Acamprosate has evidence of efficacy in AUD and is not recommended in Child–Pugh C cirrhosis. Naltrexone is well tolerated in compensated cirrhosis, but dose-dependent hepatotoxicity has been demonstrated in obesity trials and monitoring of liver function tests is recommended. Disulfiram can also lead to hepatotoxicity and is not recommended in advanced liver disease. In summary, abstinence reduces the risk of hepatic decompensation, HCC, and mortality in ALD patients. The combination of comprehensive medical care, pharmacotherapy, and psychosocial interventions are more likely to result in abstinence.

Microbiota in portal hypertension and HCC

腸道微菌叢在門脈高壓及肝癌的角色

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Humans harbor nearly 100 trillion gut bacteria that contribute to digestion and intestinal homeostasis. The diverse composition and stable amount of gut microbiome are also essential to keep systemic homeostasis and modulate the innate and adaptive immune systems. Dysbiosis, defined as the imbalance between protective and harmful bacteria both in quality and quantity, and the alteration of intestinal homeostasis will lead to many disorders. Considering 75% of hepatic blood is supplied by the portal vein that not only carries nutrients, but also translocated microbial products and bacteria; gut dysbiosis is considered to participate in the pathogenesis of hepatic steatosis, inflammation and fibrosis via the process of bacterial translocation and multiple interactions with the host's immune system. The alteration of microbial composition and function was also reported to worsen the portal hypertensive complications or even contribute to the hepatic carcinogenesis. Besides, some evidences imply that gut microbiota would have the potential to modulate tumor responses to immunotherapies. In this topic, we will review the microbiota–liver axis and its therapeutic potential in cirrhotic portal hypertension and hepatocellular carcinoma (HCC).

Management of portal hypertension in patients with HCC

肝癌患者門脈高壓之治療

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Portal hypertension (PHT) and hepatocellular carcinoma (HCC) are among the major complications of cirrhosis. The prognosis of portal hypertension has improved in these decades. Nevertheless, coexitence of PHT and HCC remains a challenging issue, especially in the era of novel systemic therapies for HCC. In patients with early HCC, PHT ranged from 35% to 52%. In patients with advanced HCC, the prevalence is probably higher than in early HCC. HCC could increase portal pressure through the presence of arteriovenous shunting within the tumor and modifications of liver architecture.

The presence of HCC is associated with a poor prognosis in patients with gastroesophageal varices. Both the risk of bleeding and the rebleeding rates are high in the presence of HCC, especially in the presence of portal vein thrombosis. In the setting of primiary prophylaxis of variceal bleeidng, endoscopic variceal ligation (EVL) is superior to propranolol in patients with HCC. The benefits of EVL on esophageal variceal bleeding and overall survival may be limited to patients with BCLC stage A/B but not to those with BCLC stage C/D. Secondary prophylaxis of acute variceal bleeding was associated with decreased need of transfusion and improved survival, which is more prominent in Child A and B class patients. Transjugular intrahepatic porto-systemic shnunt could be considered when needed in cirrhotic patients with Milan-In HCC to improve survival and as a bridge to liver transplant.

In the HCC patients receiving atezolizumab-bevacizumab treatment, bleeding events were more frequently observed than sorafenib. Banding ligation is indicated in both primary prophylaxis and seconcary propbylaxis of variceal bleeding. A 4-week ligation interval is usually recommended because of the concern of delay post-banding ulcer healing in patients on bevacizumab. Primary prophylaxis should be started before initiation of systemic therapy. In case of portal vein thrombosis, anticoagulant therapy, including new oral direct-oral anticoagulants, are not contraindicated.

Malnutrition, frailty, and sarcopenia in patients with portal hypertension and HCC

營養不良、虛弱及肌少症對門脈高壓及肝癌的影響

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Cirrhosis predisposes patients to malnutrition, frailty, and sarcopenia. While these constructs are interrelated and, in practice, are often recognized simultaneously in a single patient, these constructs have distinct operational definitions: 1. Malnutrition represents the imbalance of nutrients that causes measurable adverse effects on the body and/or outcomes; 2. Frailty is the phenotypic representation of impaired muscle function; 3. Sarcopenia is the phenotypic representation of loss of muscle mass. One can appreciate that malnutrition is a dominant factor that can lead to the clinical phenotypes of frailty and sarcopenia, but there are other many other contributing factors.

Many tools exist to measure frailty and sarcopenia in patients with cirrhosis in clinical practice. The only cirrhosis-specific tool is the Liver Frailty Index, comprised of hand grip strength, chair stands, and balance. Sarcopenia can be assessed using psoas or skeletal muscle index on cross-sectional imaging, although other methods such as bioelectrical impedance analysis (BIA), thigh ultrasound, and dual-energy X-ray absorptiometry (DXA) can be used. Numerous studies have demonstrated strong association of either frailty or sarcopenia with adverse outcomes in patients with cirrhosis, in excess of underlying liver disease severity, portal hypertensive complications, and severity of HCC.

What makes frailty and sarcopenia such a valuable predictor of adverse outcomes is that it is potentially modifiable—and even preventable—with interventions targeted at nutrition and movement. Improving frailty and sarcopenia have been associated with improved outcomes in patients with cirrhosis.

Updates in prediction and management of HCC recurrence after curative treatment

肝癌治癒後再復發的預測及治療

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The risk of hepatocellular carcinoma (HCC) recurrence remains notably elevated following curative treatment, with rates nearing 60% to 70% at the 5-year mark post-treatment. Identifying patients at high risk of recurrence has emerged as a pivotal concern for guiding adjuvant therapy. HCC recurrence is commonly categorized as either early recurrence (within 2 years post-treatment) or late recurrence (occurring after 2 years). Tumor-related factors such as size, number, microvascular invasion, and AFP levels are established predictors of early recurrence, while host and viral factors like liver fibrosis, inflammation, and viral activity commonly predict late recurrence. Recent advancements have unveiled several novel biomarkers, encompassing both serum biomarkers and molecular signatures, which exhibit correlations with HCC recurrence. Leveraging these predictors, various prognostic models have been introduced to forecast HCC recurrence. The advent of artificial intelligence (AI) and machine learning (ML) technologies has ushered in a new paradigm in HCC diagnosis and management. Recent investigations have underscored the superior predictive efficacy of AI-derived models over conventional clinical models in anticipating HCC recurrence. Encouraging results from the IMbrave050 trial have highlighted the efficacy of adjuvant immunotherapy in high-risk patients post-curative treatment. Concurrently, numerous clinical trials exploring adjuvant and neoadjuvant therapies aimed at mitigating HCC recurrence risk are underway. This lecture aims to provide an updated overview of recent strides in predictive biomarkers, prediction models for HCC recurrence post-curative treatment, and the landscape of adjuvant and neoadjuvant therapies for HCC management.

Refining treatment strategies in intermediate-stage HCC in the era of immunotherapy

免疫治療在中期肝癌的角色

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Background

The paradigm shift has happened in the treatment of hepatocellular carcinoma (HCC) due to the development of systemic chemotherapies. As the 1st-line therapy, immune-combination therapy including atezolizumab plus bevacizumab is mainly used. And as the effective anti-angiogenic drug, lenvatinib is also used. A decade ago, the treatment for intermediate HCC is very limited, the only treatment was transcatheter arterial chemoembolization (TACE). However, now we have many therapeutic choices. Therefore, treatments for intermediate HCC are becoming complicated. In the era of chemo-diversity, we need to find the best therapeutic strategy for intermediate HCC.

In the era of chemo-diversity, the main therapeutic strategy is sequential drug therapy. In sequential drug therapy, we need to know how to maximize the effects of each drug and which drugs should be used in sequential drug therapy. In this presentation, I would like to introduce how to maximize the effects of lenvatinib and atezolizumab plus bevacizumab combination therapy and the effects of altering tumor immune microenvironments (TIME) in each systemic drug and locoregional treatments including TACE and HAIC.

Results

＜ ***Lenvatinib*** ＞

To maximize the effects of lenvatinib, refinement of the administration schedule is important. Generally, lenvatinib is administered every day without any rest. However, the 5 days-on/2 days-off method, the weekends-off method, is useful for maintaining anti-tumor effects with tolerability. And combination with TACE is also useful to aim for complete response and maintenance of treatment duration of lenvatinib. A combination therapy of lenvatinib and TACE can be used for TACE unsuitable or refractory HCC to aim for a complete response.

＜ ***Atezolizumab plus Bevacizumab*** ＞

To maximize the effects of ATZ+BEV, we need to know about the management of adverse events (AEs) in ATZ+BEV. The AEs of special interest in ATZ+BEV are gastrointestinal (GI) bleeding and proteinuria, which are bevacizumab-related AEs. We should have an endoscopy criteria before administration of ATZ+BEV and have to prevent GI bleeding from oesophageal varix. To manage bevacizumab-related AEs, there are two effective methods, BEV-skipping and BEV-dose reduction.

Immune combination therapy is becoming a main actor in the treatment of HCC, and the TIME is attracting attention. Recent studies reveal that tyrosine kinase inhibitors including lenvatinib and

locoregional treatments including TACE and hepatic arterial infusion chemotherapy (HAIC) can alter the TIME from Immune “cold” to “hot”.

Conclusion

In the treatment of intermediate HCC, TACE is still at the center of treatment. However, to maximize the effects of each treatment, we need to understand more about systemic chemotherapies.

Intra-arterial therapy for HCC

肝癌的經動脈給藥治療

Po-chin Liang

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Intra-arterial therapy for HCC, cover wide range from BCLC stage 0~C. TACE is usually indicated for intermediate stage HCC with palliative intent, However, for very early or early HCC, superselective TACE with PV visualization can achieve curative effect, if not suitable for ablation, resection or transplantation. Otherwise, TAE with lipiodol tagging for HCC, followed by ablation is also with curative intent. DEB-TACE is suggested for BCLC B2 substage with bilobar multiple HCCs, or with severe side effect of cTACE. Y90 SIRT(or TARE) can play a role in early HCC with curative intent with radiation segmentectomy, if not suitable for ablation, resection, or transplantation. Y90 SIRT also can be bridging to transplantation to reduce dropout from waiting list, or downstaging to resection or ablation with the added benefit of achieving hypertrophy of the future liver remnant. Y90 SIRT can be salvage after TACE failure for intermediate stage HCC. For BCLC C stage HCCs with branch PV thrombosis, Y90 SIRT can have survival benefit , if refractory to systemic therapy. HAIC with infusion chemotherapy agent into hepatic artery, to increase local treatment effect, and decrease systemic side effect, and because no embolization of hepatic artery, so it is also suitable for HCC with main PV thrombosis. Now Atezo-Bev is 1st line systemic therapy for advanced and certain intermediate stage HCC, according to BCLC stage system 2022, with response rate near 30%. HAIC can be salvage if Atezo-Bev failure, either intermediate or advanced stage HCC. Otherwise, combine HAIC with Atezo-Bev as 1st treatment for advanced or intermediate stage HCC, have promising effect in our limited experience, it need further validation in the future investigation.