INTRODUCTION

Chronic hepatitis C (CHC) is a major public health problem and is an important cause of preventable death and morbidity from chronic liver disease1. Interestingly, 2014 marks the 25th anniversary of the identification of the hepatitis C virus (HCV). Globally, an estimated 185 million people have been infected with the HCV, with 350,000 dying each year from complications of the disease2-3. The prevalence of CHC worldwide is 2.8% with 1.4% in high-income Asia-Pacific countries and 2% in South East Asia2. In Malaysia, the incidence rate of CHC is 6.8/100,000 population in 20134.

In United States, CHC is the commonest cause of death from liver disease and the leading indication for liver transplantation5. It is anticipated that an increasing number of people are likely to die from HCV-related liver cirrhosis, liver failure or liver cancer over the next 2 decades6. Most patients with CHC are asymptomatic. 55-85% of patients with CHC will progress to chronic liver disease if left untreated. 15-30% of these patients will develop cirrhosis within 20 years and 2-4% will die of liver cancer7-10. As most patients are unaware of their infection status, there is an urgent need to screen patients especially those at risk such as those who have received blood transfusions, tissue and organ transplantation before the introduction of routine blood screening in 1995, intravenous drug users, those with HIV infection, health care workers, current sexual partners of HCV-infected persons and patients on haemodialysis. Although there is no vaccine currently available for hepatitis C, there is still hope for a cure with the recent breakthrough discovery of new drugs that can provide a cure for patients with chronic hepatitis C.

HCV is a positive-stranded RNA-enveloped virus belonging to the Flaviviridae family. The HCV genome was identified and cloned in 198911. HCV circulates as a heterogeneous population or quasispecies which differ in nucleotide sequence by 1-5%. HCV undergoes rapid mutation in a hypervariable region of the genome coding for the envelope proteins and escapes immune surveillance by the host, which helps explain the development of chronic infection in HVC-infected patients12.

The hepatitis C virus has at least 6 major genotypes (1-6) based on a sequence divergence of 30% among isolates13. Genotype 1 is common in USA, Europe and Japan, genotype 3 in India, the Far East and Australia, genotype 4 in Africa and the Middle East, genotype 5 in South Africa and 6 in Hong Kong, Vietnam and Australia14-15. Some genotypes are easier to treat than others. In Malaysia the common genotypes are genotype 3 and 1, based on tests conducted at the NATA-accredited Molecular Research Laboratory of the Malaysian Liver Foundation (MLF). HCV genotyping should be performed in all HCV-infected persons prior to treatment to establish the dose and duration of therapy and estimate the likelihood of response to treatment.

DIAGNOSIS OF CHC

The diagnosis of CHC is made after full history-taking, complete physical examination and by performing basic laboratory tests, serologic assay to detect anti-HCV antibody followed by molecular assays to detect or quantify HCV RNA. The purpose of taking the history and conducting a thorough physical examination is to exclude other liver diseases, ascertain the extent of the underlying liver disease and evaluate the patient’s eligibility for treatment. A history of alcohol consumption, blood transfusion, sexual habits and existence of metabolic diseases associated with fatty liver, signs of chronic liver disease, and complications of cirrhosis (e.g. ascites or haematemesis) must be sought. Basic laboratory tests that are required include complete blood counts, serum albumin, alanine and aspartate transaminases, alkaline phosphatase, prothrombin time, renal function tests, tests for hepatitis A, B and HIV and tests to exclude other liver diseases. The diagnosis will be supported by a positive anti-HCV antibody and confirmed by detectable HCV RNA. HCV RNA detection and quantification are important for diagnosis and management of patients with CHC. HCV genotyping tests have now become necessary and should be performed before treatment is commenced as it would guide the dose and duration of therapy and estimate the likelihood of response. The utility of a routine liver biopsy is still being debated but would be useful to establish the stage of fibrosis for prognostic purposes or to make decisions regarding treatment. Non-invasive measures (e.g. Fibroscan) to define the presence or absence of advanced fibrosis are now available and may obviate the need for a liver biopsy in some patients. Prompt treatment is needed for patients with advanced fibrosis as they are at the greatest risk of disease progression.

TREATMENT

The goal of treatment is to eradicate HCV by achieving a sustained viral response (SVR), defined as the absence of HCV RNA by polymerase chain reaction six months after stopping treatment16. SVR is associated with a 99% chance of being HCV RNA negative during long term follow-up and patients who achieve SVR can therefore be considered cured of HCV infection and this would mean a reduced incidence of disease progression (cirrhosis, end-stage liver disease and hepatocellular carcinoma), improve quality of life and significantly lower all-cause mortality17. The current treatment for patients with CHC is a combination of Pegylated interferon (IFN) and Ribavirin (RBV). Patients with genotype 2 or 3 will...
be treated for 24 weeks while those with genotype 1 will receive a longer duration of 48 weeks. The former is expected to achieve higher SVR rates (80%) compared with the latter (40-50%)\(^\text{17-21}\). Predictors of SVR following treatment with Pegylated IFN and RBV include viral factors, patient-related factors and treatment-related factors. Viral factors include HCV genotype and, to a lesser extent, the baseline viral load. Higher response rates are seen in patients with genotypes 2 or 3 than genotype 1, asuddled to earlier and in those with lower baseline viral loads (<600,000 to 800,000 IU/mL)\(^\text{22}\). Patient-related factors associated with SVR include race, IL28B polymorphisms and age. Asians have the highest response rates compared with the African Americans who have lower response rates than whites, probably because of variations in sites adjacent to the IL28B gene\(^\text{23-24}\). The IL28B gene encodes interferon lambda, which is involved in viral resistance and is up-regulated by interferons. IL28B polymorphisms are strong independent predictors of viral responsiveness to treatment with IFN and RBV. Numerous studies have also shown that patients with the CC genotype at the rs12979860 polymorphic site have higher SVR rates than patients with the CT or TT genotypes. Patients with the TT genotype at the rs8099917 polymorphic site have higher SVR rates than patients with the GT or GG genotypes. Asians appear to be associated more with the CC genotype\(^\text{25-30}\).

Other factors associated with higher SVR rates include younger age, absence of bridging fibrosis or cirrhosis, absence of significant (>33 percent) hepatic steatosis and interestingly and coffee consumption\(^\text{31-32}\). Treatment-related factors include the use of weight-based dosing of RBV, maintaining full dose therapy and treatment compliance. Changes in the viral load during treatment are also associated with an SVR. Once treatment is commenced, doctors can predict whether the patient can achieve SVR or otherwise by observing the virologic response at 12 weeks of therapy (Early virologic response or EVR) and probably even earlier ( Rapid Virologic response). It will be possible therefore to discontinue treatment for patients who are unlikely to respond. An early virologic response (EVR) is defined as at least a 2 log (10) reduction in HCV RNA compared to baseline HCV RNA level (partial EVR) or undetectable HCV RNA (complete EVR) at week 12. An SVR is unlikely in patients who fail to attain an EVR (less than 2 percent) with a negative predictive value that approaches 100 percent. SVR is achieved in approximately 65% among patients who exhibit EVR and those with a complete EVR can achieve SVR of up to 72%\(^\text{33-34}\). The likelihood of achieving an EVR is significantly lower in those with genotype 1, those with a baseline HCV RNA level greater than 800,000 IU/mL, and those with poor compliance to therapy within the first 12 weeks. A rapid virologic response (RVR), defined as undetectable HCV RNA at week 4 of therapy, is a strong predictor of an SVR and may allow shortening the treatment period for genotypes 2 and 3 and possibly genotype 1 with low viral load. Other useful treatment parameters include the End of treatment response (EOT), defined as undetectable HCV RNA at the end of 24 or 48 weeks of treatment; viral breakthrough, defined as reappearance of HCV RNA in serum while still on therapy; relapse, defined as reappearance of HCV RNA in serum after treatment is discontinued; non-responder, defined as failure to clear HCV RNA from serum after 24 weeks of treatment; null responder indicating failure to achieve as decrease in HCV RNA by less than 2 logs from baseline after 24 weeks of treatment and partial responder referring to more than a 2 log decrease in HCV RNA from baseline at week 12 of therapy but with positive HCV RNA at week 24\(^\text{16}\).

The current treatment for CHC is not ideal as IFN has to be injected and may cause serious side effects which include depression, anorexia, flu-like illness, low blood counts and thyroid abnormalities. Patients with psychiatric illnesses or autoimmune disease are contraindicated for IFN. Better alternatives are therefore being sought. There was a breakthrough in 2011 with the approval of 2 direct acting antiviral drugs (DAAs), Boceprevir\(^\text{35-36}\) and Telaprevir\(^\text{37-38}\), which improve SVR specifically for patients with genotype 1 when used in combination with Pegylated IFN and RBV, achieving SVR of 40-44% to 68-75% in those who have not been previously treated. Their use however was associated with frequent side effects and drug interactions and the response rates amongst cirrhotics remain low. Boceprevir and Telaprevir are both first wave, first generation NS5-4A protease inhibitors. Two others, Simeprevir (second wave, first generation NS3-4A protease inhibitor)\(^\text{39}\) and Sofosbuvir (nucleotide analogue inhibitor of the viral polymerase) have been approved in USA in 2013 and Europe in 2014\(^\text{40}\). Following the approval of these 2 new drugs, four treatment combinations are now possible for patients with CHC, 2 IFN-containing regimens and 2 IFN-free combinations. The two IFN-containing regimens include the triple combination of Peg IFN, RBV and Simeprevir for 24 to 48 weeks for patients with HCV genotype 1, which can achieve an SVR of 80% and the triple combination of Peg IFN, RBV and Sofosbuvir for 12 weeks for patients with genotype 1-6, which can achieve an SVR of at least 90%. The IFN-free options include a combination of Sofosbuvir and RBV for 12 weeks for patients with genotype 2, achieving an SVR of 95% for non-cirrhotics and the combination of Sofosbuvir and RBV for 24 weeks for genotype 3, achieving an SVR of 85% in non-cirrhotics. Cirrhotics can only achieve an SVR of 60% with the latter combination\(^\text{41-47}\). Sofosbuvir in combination with Ledipasvir (NS5A inhibitor) as a fixed dose combination in a tablet, with or without RBV, has been shown to cure 95-100% of patients with genotype 1 HCV, given for 8 to 12 weeks, irrespective of whether they have been treated previously or not or whether there is associated compensated cirrhosis\(^\text{48}\).

Since the discovery of the new DAAs, there has been a phenomenal increase in the number of clinical trials involving new agents and targets. More than 60 direct-acting antivirals (DAAs) and host-targeted agents (HTAs) are in various stages of clinical development and over 30 of them are in phase 2 or 3 trials for HCV infection. These oral, interferon-free combinations of drugs are expected to cure more than 90% of infections. The new DAAs include NS3-4A protease inhibitors such as Simeprevir, Faldaprevir, Asunaprevir and Danoprevir, Nucleoside /nucleotide analogues RdRp inhibitors such as Sofosbuvir, Non-nucleoside RdRp inhibitors such as Lomivir, NSSA inhibitors such as Daclatasvir and Ledipasvir and Cyclophilin A inhibitors such as Alisporivir\(^\text{49}\).

It is conceivable that from the year 2015, interferon-containing combinations will be replaced by interferon-free regimens with cure rates of more than 90%. A total of 11 DAAs from all four major drug classes are expected to reach market by the end of 2016. Response to patients with genotype 2 is still better than
genotype 3. It is hoped that DAAs with high genetic barrier to the development of drug resistance can offer better treatment options for difficult to treat patients groups such as those with advanced liver diseases or co-infection with HBV or HIV. More complex regimens involving four or more drugs including the use of IFN and RBV, however, may still be required for selected patients. The ideal drug or combination of drugs must be one that can be given orally once or daily, with few side effects, minimal drug interactions and resistance, short treatment duration and effective against all major genotypes.

The discovery of more effective therapies for CHC, while bringing a lot of hope for patients with CHC, is tempered with some pertinent issues that have to be seriously addressed. These include identifying patients at risk, access to care and the high costs of these new drugs. The initial price of Sofosbuvir and Simeprevir is USD84,000 and USD66,000 respectively and a combination of both is USD150,000 for a 12-week treatment course. Although the new oral agents are more effective and easier to administer, they are not affordable to most patients because of the exorbitant costs. It is possible that the costs of these drugs may become lower with the anticipated approval of more new oral agents in the ensuing months. Let us hope that efforts to reduce the costs of the new oral combination drugs for CHC will bear fruit.

HCV is a blood-borne infection with no known natural non-human reservoir and is cure is therefore possible. The unprecedented discovery of many more effective oral drugs can offer hope of cure to patients infected with this disease. The Ministry of Health of Malaysia should take the cue from a report published by the Institute of Medicine in 2010 where it was clearly enunciated that more needs to be done by individual countries to enhance screening programmes, identify patients at risk, link them to trained health care providers and make treatment affordable to them. This would involve a revamp of our public health policy and a strong commitment from our Government to increase financial and other resources to train and support our public health specialists, primary care physicians, general physicians, gastroenterologists and hepatologists so that they are able to provide the linkage and network between screening of individuals, identification of those infected with hepatitis C and provision of definitive treatment for those who are eligible. Only then can we confidently proclaim that cure for chronic hepatitis C is possible.

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