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MESSAGE FROM THE PRESIDENT

DR. RAMESH GURUNATHAN

Welcome faculty and delegates to the Annual Scientific Meeting of The Malaysian Society of Gastroenterology and Hepatology 2013. This year's meeting takes us to the Pearl of the Orient, where we have lined up an interesting scientific program. The present committee will finish their 2 year term at this this meeting. It has been a pleasure to be part of this society and I would like to take this opportunity to thank all my committee members who have strived hard for benefit of our members.

This year we have lined up world class speakers with a wide range of topics to suit everyone. The 13th MSGH Oration will be given by none other than our very own Prof. Dato' KL Goh on his topic: Asia at the the crossroads: Changing patterns and emerging diseases. The 10th Panir Chelvam Memorial Lecture will be given by Michael Kamm which will equally be interesting.

The Malaysia Night as always will promise to be an exciting event to unwind and enjoy. I do hope this year's meeting will continue to be as successful as our previous meetings and I will also like to wish the incoming committee all the very best. MSGH

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FROM THE EDITOR

I invite MSGH members and readers to contribute articles, news on MSGH events and gastrointestinal (GI) updates to the MSGH Bulletin. This issue contains news on the upcoming GUT 2013 and several interesting articles on the liver and GI diseases. MSGH has also started the electronic version of the MSGH bulletin. The inaugural issue of the MSGH e-bulletin was produced on 19 December 2012, and we shall continue to have more in the future.

Dato' Dr. Mazlam Mohd Zawawi

GUT 2013, PENANG

DATO' DR. TAN HUCK JOO
Scientific Chairman
Gut 2013 - Annual Scientific Congress of the MSGH

The Annual Scientific Congress of MSGH - Gut 2013 will be held at the G-Hotel, Penang from the 23rd Aug 2013 to 25th Aug 2013. Once again, we have some of the most outstanding speakers joining us this year.

Prof. KL Goh has been unanimous nominated by the organizing committee to be the distinguished lecturer for this year's MSGH Oration. Prof. Goh has been the Scientific Chairman of the Gut Meetings for many years and is also the main organizer for the very successful UMMC/MSGH Advanced Endoscopy Workshop. He is currently also the President of APAGE, and Vice President of WGO. His lecture is "Asia at the crossroad: Changing patterns and emerging diseases."

Professor Michael Kamm, an outstanding gastroenterologist and researcher, currently a Professor Of Gastroenterology at St Vincent Hospital, Melbourne will deliver the 10th Panir Chelvam Memorial Lecture. Prof. Kamm was the Professor of Gastroenterology at the world renowned St Mark Hospital in London. He is of course one of the world leading expert in IBD and chronic constipation. He is named lecture is on "Achieving the optimal balance between drug therapy and surgery in inflammatory bowel disease." He will also talk on "Best use of biologic therapy - anti-TNF therapy and beyond".

Vijay Shah, a Professor from Mayo Clinic, Rochester, USA, is an expert in portal hypertension and alcoholic liver disease. He will be delivering a lecture on "molecualr targets of HCC therapies" in the HCC symposium and "Variceal screening and primary prophylaxis - what is new?" in the portal hypertension symposium. In addition, he will also be an expert panelist in the Case discussion on portal hypertension.

Kenneth McColl, Professor of Gastroenterology at the University of Glasgow, with several landmark studies under his belt, will be sharing with us the "Changing epidemiology of gastric cancer". He will also talk to us about acid pocket - what is their clinical significance in dyspepsia?"

Bjorn Rembacken is a consultant endoscopist from Leeds, UK. He is an expert in colonic polypectomy. Bjorn will speak on "therapeutic endoscopy in IBD" and "Surveillance of precancerous gastric lesions - what is the evidence?" He will of course be one of the expert panelists in the colonic neoplasia case discussion.

David Peura is a professor of Gastroenterology, University of Virginia, USA. He was the President of American Gastroenterological Association. He was the winner of the Julius Friedenwald Medal, the highest honor awarded by the AGA. He has been involved in clinical investigation on acid peptic disorders, particularly peptic ulcer disease, and *Helicobacter pylori* and its role in ulcer pathogenesis. David will share with us "Chemoprevention in gastrointestinal cancers."

Alan Barkun is the Chief Quality Officer of the Division of Gastroenterology at McGill University, Quebec, Canada. Alan has published more than 400 peer-reviewed articles and abstracts. His research interest varies from emerging digestive endoscopic techniques, GI Bleed, pancreatobiliary disorders and colorectal cancer screening. Alan will deliver a lecture on "Balancing the risk and benefit of antiplatelet therapy in clinical practice". He will also be the panelist in the case discussions.

Francis Chan is Professor of Medicine at the Chinese University of Hong Kong. With many landmark studies in the Lancet, New England Journal of Medicine, there is no one else more qualify to talk to us about the "Strategies to reduce GI risk of COX2i/NSAID". He will also conduct an interactive Meet-The-Expert session on "Minimizing

upper GI bleed in patients commencing anticoagulation therapy".

Justin Wu is Professor of Gastroenterology from the Chinese University of Hong Kong. Justin is an expert in functional gut disease. He will speak to us on "Stratifying treatment of functional dyspepsia according to Rome III criteria".

Ng Siew Chien is Associate Professor of Medicine at the Chinese University of Hong Kong. Malaysian in origin, Prof. Ng is an expert in IBD. She will share with us the "Genetics of IBD in Asia". and "How to manage anemia and osteoporosis in IBD".

Yoshiaki Takeuchi is Associate Professor of Gastroenterology from Showa University School of Medicine, Japan. He will deliver a lecture on "Gastric emptying in GERD and functional dyspepsia management".

Takeshi Sano is one of the world leading expert in gastric cancer resection from Cancer Institute Hospital, Tokyo, Japan. He will lecture on "gastric cancer staging and treatment" and cardio-esophageal junction tumor: treat as esophageal or gastric malignancy?"

David Kwon is Associate Professor in Surgery and a liver transplant surgeon from Samsung Medical Centre, Seoul, Korea. He will talk on "Selection criteria for salvage liver transplantation after liver resection for HCC recurrence - Looking beyond size and number".

Chien RN is Professor of Hepatology at the Chang Gung Memorial Hospital and University, Taiwan. He will be speaking to us on "Stratifying risk for complications in hepatitis B patients". and "Optimizing HBV therapy - is there a role for combination therapy?"

Pierce Chow is an eminent liver surgeon from Singapore General Hospital. His topic is on "Managing small liver nodule in cirrhotic patients - resection, transplant or others?" and "Multidisciplinary management of HCC"

Francis Seow Choen is a senior colorectal surgeon from Singapore. His lecture is "Is there still a role for the surgeon in Crohn's?" and "Managing colonic perforation".

Mark your calendar for this important event. See you all in Penang! MSGH

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STATEMENTS OF THE MALAYSIAN SOCIETY OF GASTROENTEROLOGY & HEPATOLOGY AND THE NATIONAL HEART ASSOCIATION OF MALAYSIA TASK FORCE 2012 WORKING PARTY ON THE USE OF ANTIPLATELET THERAPY AND PROTON PUMP INHIBITORS IN THE PREVENTION OF GASTROINTESTINAL BLEEDING

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The working party statements aim to provide evidence and guidelines to practising doctors on the use of antiplatelet therapy and proton pump inhibitors (PPIs) in patients with cardiovascular risk as well as those at risk of gastrointestinal (GI) bleeding. Balancing the GI and cardiovascular risk and benefits of antiplatelet therapy and PPIs may sometimes pose

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a significant challenge to doctors. Concomitant use of anti-secretory medications has been shown to reduce the risk of GI bleeding but concerns have been raised on the potential interaction of PPIs and clopidogrel. Many new data have emerged on this topic but some can be confusing and at times controversial. These statements examined the supporting evidence in four main areas: rationale for antiplatelet therapy, risk factors of GI bleeding, PPI–clopidogrel interactions and timing for recommencing antiplatelet therapy after GI bleeding, and made appropriate recommendations.

KEY WORDS: antiplatelet therapy, gastrointestinal bleeding, proton pump inhibitor.

INTRODUCTION

This working party statement was developed by the Malaysian Society of Gastroenterology and Hepatology (MSGH) and the National Heart Association of Malaysia (NHAM) to provide evidence and guidelines to practising doctors on the use of antiplatelet therapy and proton pump inhibitors (PPIs) in patients with cardiovascular (CV) risk as well as those at risk of gastrointestinal (GI) bleeding. Many new data have emerged on this topic but some can be confusing and at times controversial. The statements of the working party aimed to address some of these issues and clarify them as much as possible. It is our hope that they will benefit not only doctors practising in Malaysia but also those in other parts of the world.

Antiplatelet drugs are widely used in the prevention and management of atherosclerotic CV disease. Aspirin is the most commonly used antiplatelet agent because of its wide availability, low cost and good efficacy. It works by inhibiting the enzyme cyclooxygenase (COX) and reducing the production of thromboxane A2, a stimulator of platelet aggregation.[1] It is used in the acute setting of myocardial infarction (MI) as well as in the primary and secondary prevention of CV diseases.[2] The other class of antiplatelet agent used is the adenosine diphosphate (ADP) receptor inhibitors. They can be further divided into thienopyridines such as ticlopidine, clopidogrel, prasugrel and elinogrel, and non-thienopyridines such as ticagrelor and cangrelor. These classes of drug are P2Y12 antagonists binding to the P2Y12 receptors located on the surface of the platelet cell, which in turn lead to the binding of ADP, thus inhibiting platelet aggregation.[1] Ticlopidine was the first thienopyridine introduced to clinical practice. It has proven to be an effective antiplatelet drug but its potential severe side effects such as neutropenia and thrombotic thrombocytopenic purpura had limited its use and has largely been replaced by clopidogrel. Thienopyridines are less likely to cause GI hemorrhage and GI upset.[3] A landmark trial (CAPRIE)[4] has demonstrated that clopidogrel alone is superior to aspirin using a composite end point of ischemic stroke, MI and peripheral arterial disease. On subgroup analysis, however, no therapeutic advantage has been found of clopidogrel monotherapy over aspirin in preventing ischemic stroke or MI.

Table 1: Summary of findings and recommendations on antiplatelet therapy and gastrointestinal (GI) bleeding

A. Rationale for antiplatelet therapy
   1. Clopidogrel and aspirin dual therapy is superior to aspirin alone in reducing CV events in ACS and PCI but significantly increases the risk of GI bleeding.
   2. Dual antiplatelet therapy with prasugrel or ticagrelor (and aspirin) is more effective than clopidogrel and aspirin in preventing major CV events in ACS with PCI, but it increases the risk of major bleeding.

B. Antiplatelet and GI bleeding
   1. Antiplatelet drugs increase the risk of GI bleeding.
   2. PPIs are superior to H_2RA in the primary and secondary prevention of aspirin-induced ulcer.
   3. *H. pylori* detection and eradication is recommended for high GI bleeding risk patients before commencing long-term aspirin.
   4. Continuing PPIs after *H. pylori* eradication is superior to *H. pylori* eradication alone in preventing recurrent ulcer bleeding in patients on aspirin.
   5. In patients with previous upper GI bleeding, PPIs should be added to antiplatelet therapy to prevent recurrent ulcer bleeding.
   6. Patients with high risk for GI bleeding requiring antiplatelet therapy should be on long-term PPIs.

C. PPI–clopidogrel interaction
   1. PPIs inhibit activation of clopidogrel via CYP2C19 pathway based on in vitro studies.
   2. There is no consistent evidence that any single particular PPI interacts adversely with clopidogrel.

D. Recommencing antiplatelet therapy following bleeding
   1. Aspirin should be recommenced early to reduce CV mortality although the risk of GI bleeding increases

CV, cardiovascular; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; H_2RA, H2-receptor antagonist; *H. pylori*, *Helicobacter pylori*; CYP2C19, cytocrhome P450 2C19.

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Balancing the GI and CV risk and benefits of antiplatelet therapy and PPIs may pose a significant challenge to doctors. The concomitant use of antisecretory medications has been shown to reduce the risk of GI bleeding but concerns have been raised on the potential interaction of PPIs and clopidogrel. The following statements by MSGH and NHAM are based on the current available evidence to address the different aspects of antiplatelet therapy and GI bleeding: the rationale for antiplatelet therapy, the risk of GI bleeding associated with antiplatelet therapy, PPI–clopidogrel interaction and the timing for recommencing antiplatelet therapy following GI bleeding (Table 1).

RATIONALE OF ANTIPLATELET THERAPY

1. Clopidogrel and aspirin dual therapy is superior to aspirin alone in reducing CV events in acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) but significantly increases the risk of GI bleeding

In patients presenting with non-ST elevation ACS the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial[5] demonstrated an 18% lower incidence of death, MI or stroke in patients given dual antiplatelet therapy (clopidogrel plus aspirin) than in those treated with aspirin alone. Not unexpectedly, there were more patients with major bleeding in the dual therapy group (3.7%) than in the aspirin monotherapy group (2.7%) (relative risk [RR] 1.38, 95% confidence interval [CI] 1.13–1.67; $P = 0.001$). A Cochrane Database Systematic Review[6,7] also showed a clear benefit of dual therapy in patients with acute non-segment (ST) elevation coronary syndrome but the evidence was not good for high CV-risk patients, that is, those with multiple risk factors for ischemic heart disease but who did not present acutely with coronary syndrome.

In patients presenting with acute ST elevation MI, both the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)[8] and the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction Trial (CLARITY-TIMI)[9] showed clearly the benefit of dual antiplatelet therapy *vs* aspirin monotherapy, with an 8% and 31% lower incidence of death, MI and stroke, respectively. Dual antiplatelet therapy is recommended for at least one year followed by aspirin indefinitely.

For patients with stable coronary artery disease, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) Trial[10] demonstrated that dual antiplatelet therapy with clopidogrel and aspirin is not significantly better than aspirin alone in preventing death, MI or stroke in more than 15 000 patients (secondary prevention). However, it is unknown whether dual antiplatelet therapy is superior to aspirin monotherapy as primary prevention in high-risk patients with multiple risk factors for ischemic heart disease but with no prior history of it.

Two important trials provided evidence for the benefit of clopidogrel and aspirin in patients undergoing PCI. A sub-study of CURE, PCI-CURE,[11] examined the effects of clopidogrel and aspirin dual therapy in 2658 patients with non-ST elevation ACS undergoing PCI. There was a 31% RR reduction in the incidence of CV death, MI or the need for re-vascularization in patients pretreated with clopidogrel for a mean period of 10 days. Similarly the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial[12] showed clearly the benefit of clopidogrel and aspirin with a 3% absolute reduction in death, MI or stroke compared with aspirin alone.

2. Dual antiplatelet therapy with prasugrel or ticagrelor (and aspirin) is more effective than clopidogrel and aspirin in preventing major CV events in ACS with PCI, but it increases the risk of major bleeding

The Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel – thrombolysis in MI (TRITON-TIMI 38) trial studied 13 608 patients with moderate to high risk of ACS and compared the efficacy of prasugrel with aspirin *vs* clopidogrel and aspirin in patients undergoing PCI with various stents. Prasugrel plus aspirin was found to be superior in reducing the primary end point of CV death and non-fatal MI in patients with ACS (9.9% *vs* 12.1%, $P = 0.0001$).[13] A sub-analysis of TRITON-TIMI 38 demonstrated that prasugrel reduced the primary end point in the stented cohort, both in the drug-eluting stent (9% *vs* 11.1%, $P = 0.019$)[14] and bare metal stent groups (10% *vs* 12.2%, $P = 0.003$). However, prasugrel significantly increased major bleeding and fatal bleeding when compared to clopidogrel, especially in elder patients >75 years, patients weighing less than 60 kg and those with a previous stroke or transient ischemic attack.[13]

In a multicenter double-blind randomized controlled trial (RCT), the Study of Platelet Inhibition And Patients Outcomes (PLATO), ticagrelor plus aspirin was compared with clopidogrel plus aspirin in the prevention of CV events in 18 624 patients with ACS. Ticagrelor was found to be superior to clopidogrel in reducing the primary end point of composite death from CV causes, as seen in 9.8% patients receiving ticagrelor *vs* 11.7% receiving clopidogrel ($P < 0.001$). No significant difference in major or fatal GI bleeding rates was found between the ticagrelor and clopidogrel groups,[15] although there were higher rates of fatal intracranial bleeding in the ticagrelor group. Based on these data, the American College of Chest Physicians[16] issued a recommendation of low dose aspirin plus either ticagrelor 90 mg twice daily, clopidogrel 75 mg/day or prasugrel 10 mg/day for patients with ACS undergoing PCI with stent placement.

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ANTIPLATELET AND GI BLEEDING

1. Antiplatelet drugs increase the risk of GI bleeding

There is no question that antiplatelet therapy is associated with an increased risk of upper GI bleeding.[17] Ibáñez *et al.* showed that the odds ratio (OR) for upper GI bleeding was 4.0 (3.2–4.9) for patients taking aspirin, 2.3 (0.9–6.0) for those on clopidogrel, 0.9 (0.4–2.0) for those on dipyridamole and 3.1 (1.8–5.1) for those on ticlopidine. A meta-analysis of 18 trials involving 129 314 patients evaluated the bleeding risk of antiplatelet therapy. Not surprisingly, patients on dual antiplatelet therapy were associated with an increased risk of major (RR 1.47, 95% CI 1.36–1.60) and minor bleeding (RR 1.56, 95% CI 1.47–1.66). These patients have a 40–50% increase in risk of major and minor bleeding.[18]

2. PPIs are superior to H2-receptor antagonists (H2RAs) in primary and secondary prevention of aspirin induced ulcer

Primary prevention

H2RAs have been shown to be effective as primary prevention for aspirin-induced peptic ulcer disease in average-risk patients. Taha *et al.*[19] conducted a phase III, randomized, double-blind, placebo-controlled trial to assess the effect of famotidine, an H2RA, on patients receiving aspirin who had no previous peptic ulcers at baseline. At 12 weeks, patients treated with famotidine had a lower incidence of gastric ulcers (3.4% *vs* 15%; OR 0.2, 95% CI 0.09–0.47, $P = 0.0002$), duodenal ulcers (0.5% *vs* 8.5%; OR 0.05, 95% CI 0.01–0.40, $P = 0.0045$) and erosive esophagitis (4.4% *vs* 19%; OR 0.20, 95% CI 0.09–0.42, $P < 0.0001$). This study confirmed the role of H2RAs as primary prevention in aspirin-induced ulcers.

Similarly, PPIs have also been shown to be effective as primary prevention for aspirin-induced ulcer. Yeomans *et al.*[20] assessed the efficacy of esomeprazole for reducing the risk of gastroduodenal ulcers associated with low-dose aspirin for 26 weeks. Peptic ulcer disease developed in 5.4% of the patients treated with placebo compared with 1.6% in the esomeprazole group. There were significantly fewer patients who developed erosive esophagitis in the esomeprazole group (4.4% *vs* 18.3%, $P < 0.0001$).

PPIs were found to be superior to H2RAs in the primary prevention of peptic ulcer disease, especially in those treated with multiple antiplatelet therapies. Ng *et al.*[21] conducted an RCT comparing the efficacy of famotidine and esomeprazole in preventing GI complications in patients with ACS or ST-elevation MI receiving aspirin, clopidogrel and enoxaparin or thrombolysis. Significantly more patients presented with upper GI bleeding in the famotidine group than the esomeprazole group (6.1% *vs* 0.6%, $P = 0.0052$). A retrospective analysis from the same authors[22] earlier also demonstrated that the risk of upper GI bleeding was marginally reduced by H2RAs (OR 0.43, 95% CI 0.18–0.91, $P = 0.04$) and significantly reduced by PPIs (OR 0.04, 95% CI 0.002–0.21, $P = 0.002$).

Secondary prevention

For secondary prevention of aspirin-induced peptic ulcer disease, PPIs again have been shown to be superior to H2RAs. Bardhan *et al.*[23] studied the efficacy of lansoprazole and ranitidine as a maintenance treatment for 12 months in patients known to have duodenal ulcers and who had been previously treated with either lansoprazole or ranitidine for 8 weeks. Patients treated with lansoprazole achieved a much higher ulcer healing rate than those on ranitidine (98% *vs* 89%, $P < 0.001$) and it provided more rapid symptom relief than ranitidine. For the maintenance phase, lansoprazole was found to be superior to ranitidine in the prevention of relapse (lansoprazole 30 mg, 5% of relapse and lansoprazole 15 mg, 12% of relapse *vs* ranitidine 150 mg, 21% of relapse, respectively). Similarly, Ng *et al.*[24] performed a double-blind RCT comparing high-dose famotidine and pantoprazole in preventing recurrent aspirin-related peptic ulcer. Pantoprazole was found to be superior in preventing peptic ulcer bleeding (0% *vs* 7.7%, $P = 0.0289$) and recurrent dyspepsia (0% *vs* 12.3%, $P = 0.0031$).

3. *Helicobacter pylori (H. pylori)* detection and eradication is recommended for high GI risk patients before commencing long-term aspirin

4. Continuing PPIs after *H. pylori* eradication is superior to *H. pylori* eradication alone in preventing recurrent ulcer bleeding in patients on aspirin

Table 2: Risk factors for upper gastrointestinal (GI) bleeding

Prior history of GI bleeding
Concomitant NSAIDs
Concomitant COX-2 inhibitors
Concomitant anticoagulants
Concomitant clopidogrel
Concomitant corticosteroids
Helicobacter pylori infection
Age >65 years
Short-term NSAIDs

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase.

Several risk factors for GI bleeding have been identified and reported (Table 2),[25–31] including a prior history of peptic ulcer disease, concomitant nonsteroidal anti-inflammatory

drugs (NSAIDs), short-term rather than chronic NSAIDs users, COX-2 inhibitors,[32] clopidogrel, anticoagulants,[33–35] prednisolone[36,37] or aspirin,[38,39] *H. pylori* infection and age (>65 years old).[25,26] Obviously, the more risk factors a patient possesses, the higher the risk of upper GI bleeding. By identifying and eliminating the risk factors the risk of GI bleeding could be minimized.

Chan *et al.*[40] showed that *H. pylori* eradication was as good as providing PPIs maintenance therapy in patients with a history of upper GI bleeding who were taking aspirin. The probability of recurrent bleeding at 6 months was 1.9% for patients receiving eradication therapy and 0.9% for those receiving omeprazole (absolute difference 1.0%, $P > 0.05$). However, a metaanalysis of six studies revealed that *H. pylori* eradication therapy was superior to anti-secretory non-eradication therapy without subsequent long-term maintenance anti-secretory treatment (4.5% *vs* 23.7%, OR 0.18, number needed to treat [NNT] 5) in preventing recurrent ulcer bleeding. NNT with eradication therapy to prevent one episode of rebleeding, compared with non-eradication therapy, was 5 (95% CI 4–8) with the fixed effect model. The rebleeding rate for *H. pylori* eradication group was 1.6% *vs* 5.6% in the maintenance anti-secretory therapy group (OR 0.25, NNT 20).[41] Lai *et al.*[42] further confirmed that treatment with PPIs following successful *H. pylori* eradication significantly reduces the risk of recurrent ulcer complications. In patients with aspirin-induced ulcer and successful *H. pylori* eradication, lansoprazole maintenance therapy was associated with a lower recurrence rate (1.6% *vs* 14.8%) than placebo at 12-month follow-up. It is, therefore, worth detecting and eradicating *H. pylori* infection in patients followed by PPIs maintenance in high GI bleeding risk patients who require long-term aspirin, although long-term data are lacking.

5. In patients with previous upper GI bleeding, PPIs should be added to antiplatelet therapy to prevent recurrent ulcer bleeding

Patients who have previous upper GI bleeding from any cause are at a higher risk of recurrence. For patients with aspirin-induced peptic ulcer bleeding and who need to continue with antiplatelet therapy, the initial recommendation was to prescribe clopidogrel to replace aspirin for the prevention of recurrent peptic ulcer. However, subsequent studies have confirmed that adding PPIs to aspirin was a better approach than replacing aspirin with clopidogrel to prevent recurrent peptic ulcer disease. Doggrell assigned clopidogrel to 161 patients and aspirin plus esomeprazole to 159 patients following endoscopically confirmed ulcer healing. The combination therapy with aspirin and esomeprazole was shown to be superior to clopidogrel alone in preventing recurrent ulcer bleeding (0.6% *vs* 8.1%, $P < 0.001$).[43] This finding was confirmed in an important clinical trial by Chan *et al.*[44] involving 320 patients, again showing that the combination of aspirin and esomeprazole is superior to switching to clopidogrel (the cumulative incidence of recurrent bleeding at 12 months was 8.6% and 0.7% for those on clopidogrel vs aspirin + esomeprazole, respectively; $P = 0.001$) in preventing recurrent ulcer bleeding. A similar conclusion was drawn by Lai *et al.*[45] in a different, prospective, double-blind, randomized controlled study involving 170 patients with aspirin-induced ulcer bleeding. The cumulative incidence of recurrent ulcer bleeding was 0% in the aspirin plus esomeprazole group *vs* 13.6% in the clopidogrel group ($P = 0.0019$).

6. Patients with a high risk for GI bleeding requiring antiplatelet therapy should be on long-term PPIs

Primary prophylaxis for GI bleeding is not necessary for patients with average GI bleeding risk commencing aspirin. In average risk patients starting aspirin therapy, the risk of major upper GI bleeding is increased 1.5 to 3.2 fold and the absolute rate is increased by 0.12% per year. The number needed to harm (NNH) at one year was 833 (95% CI 526- 1429).[46]

In patients at high risk of GI bleeding but who have not bled in the past, PPI should be added if they require antiplatelet therapy. RCT on the assessment of the risk of GI event comparing omeprazole *vs* placebo in patients on dual antiplatelet therapy clearly demonstrated that omeprazole significantly reduced the rate of upper GI bleeding (1.1% *vs* 2.9%, $P < 0.001$).[47]

PPI-CLOPIDOGREL INTERACTION

1. PPIs inhibit the activation of clopidogrel via the cytochrome P450 (CYP) 2C19 (CYP2C19) pathway, based on in vitro studies

Clopidogrel is a prodrug metabolized by the CYP enzyme system to form its active metabolite. PPIs may diminish the antiplatelet effect of clopidogrel by inhibiting CYP2C19 isoenzyme and therefore the conversion of clopidogrel into its active metabolite. This may explain the adverse clinical outcomes associated with the concomitant use of PPIs and clopidogrel reported previously.[48]

Gilard *et al.*[49] revealed that omeprazole significantly decreased the clopidogrel inhibitory effect on platelets. This was confirmed by Small *et al.*[50] and Sibbing *et al.*[51] O'Donoghue *et al.*[52] measured the platelet function *in vitro* in the presence of clopidogrel and prasugrel and observed an attenuation of the antiplatelet effect. However, this is not associated with adverse clinical outcome, suggesting that surrogate end points should not be used as a substitute for clinical events.

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2. There is no consistent evidence that any single particular PPI interacts adversely with clopidogrel

Studies comparing the effect of various PPIs on clopidogrel have yielded inconsistent results. Using platelet reactivity index (PRI) vasoactive stimulated phosphoprotein as a measurement for clopidogrel non- esponders, there were significantly more clopidogrel non-responders among patients taking omeprazole than those taking pantoprazole (44% *vs* 23%, $P = 0.04$, OR 2.6, 95% CI 1.2–6.2) at 1 month when Cuisset *et al.*[53] compared the effect of omeprazole and pantoprazole on the platelet response to clopidogrel after coronary stenting in 104 patients. Siller-Matula *et al.*,[54] however, did not find any difference between pantoprazole and esomeprazole in the mean PRI and platelet aggregation. They concluded that neither esomeprazole nor pantoprazole were associated with an impaired response to clopidogrel. Angiolillo *et al.*[55] performed four randomized placebo-controlled studies on 282 healthy participants to investigate the potential interaction between omeprazole and clopidogrel and if this existed, whether this effect could be mitigated by separating the dosing to 12 h apart or by increasing the dosage of clopidogrel or substituting omeprazole with pantoprazole. The studies revealed that omeprazole decreased the clopidogrel active metabolite significantly, whether it was given simultaneously, 12 h apart or with higher dosing of clopidogrel. Substituting omeprazole with pantoprazole had the least effect on active clopidogrel metabolites. Similarly Frelinger *et al.*[56] demonstrated that esomeprazole but not lansoprazole or dexlansoprazole significantly decreased the clopidogrel active metabolite and reduced the effect of clopidogrel on vasodilator-stimulated phosphoprotein PRI. Kwok and Loke[58] conducted a systematic review of 19 studies and 4693 patients on the effects of PPIs on platelet functions in patients receiving clopidogrel. Only omeprazole was implicated, whereas pantoprazole and esomeprazole did not demonstrate any significant interaction.[47]

Clinical outcome studies on the PPI–clopidogrel interaction have also been inconsistent. Although observational studies have suggested an interaction between PPI and clopidogrel with adverse clinical outcomes,[48,59–62] there are also many clinical studies that failed to show a positive association.[52,63,64] A meta-analysis of 23 studies[57] involving 93 278 patients demonstrated that PPIs use simultaneously with clopidogrel was not associated with an increase in CV risk, after adjusting for confounders. No one PPI was implicated in this analysis. The only RCT on this topic showed a significant reduction in bleeding peptic ulcer disease in patients given PPIs without an increase in CV events.[47,58]

H_2RAs had been proposed as a substitute for PPIs in patients on clopidogrel requiring peptic ulcer disease bleeding prophylaxis. A population-based retrospective cohort study[65] of 6552 patients in Taiwan, China showed that both PPIs and H_2RAs were independent risk factors for adverse outcomes. The risk of rehospitalization for ACS or all-cause mortality within 3 months of rehospitalization was 26.8% (95% CI 21.5– 33.0%, NNH = 7) in the clopidogrel plus H_2RA cohort and 33.2% (95% CI 27.8–39.4%, NNH = 5) in the clopidogrel plus PPI cohort, compared with 11.6% (95% CI 10.8–12.5%) in the clopidogrel alone cohort ($P < 0.0001$). In contrast, Tunggal *et al.*[66] demonstrated that neither esomeprazole nor famotidine reduced the platelet inhibitory effect of clopidogrel based on platelet reactivity units at baseline and at day 28. There has also been no clinical evidence to demonstrate that H_2RAs are effective in preventing peptic ulcer complications in patients taking clopidogrel.

Obviously, if there is any doubt, prasugrel[50,66] and ticagrelor[68–70] are an alternative as neither has been shown to have any significant interactions with PPIs. In an analysis of two RCTs to assess the pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel in the presence of PPIs, O'Donoghue *et al.*[52] demonstrated that the mean inhibition of platelet aggregation was significantly lower for patients on PPIs than those without after clopidogrel treatment (23.2% ± 19.5% *vs* 35.2% ± 20.9%, $P = 0.02$), whereas a more modest difference was found after prasugrel was given (69.6% ± 13.5% *vs* 76.7% ± 12.4%, $P = 0.054$). In the TRITON-TIMI 38 trial[13] to assess clinical efficacy, PPIs use was not associated with any CV risk in patients treated with clopidogrel (adjusted hazard ratio [HR] 0.94, 95% CI 0.80–1.11) or prasugrel (adjusted HR 1.00, 95% CI 0.84–1.20).

Similarly, Storey *et al.*[70] demonstrated that ticagrelor has a greater antiplatelet inhibitory effect than clopidogrel and the concomitant use of PPIs did not have any effect on ticagrelor. Goodman *et al.*[68] examined the relationship between PPIs use and 1-year CV events in patients with ACS receiving either clopidogrel or ticagrelor. Patients treated with PPIs had a higher risk of CV end points, both in the clopidogrel and ticagrelor group. A similar trend was found in patients taking other non-PPI GI drugs. However, patients without any gastric therapy had a significantly lower level of CV events (PPIs *vs* no GI treatment: clopidogrel, HR 1.29, 95% CI 1.12–1.49; ticagrelor, HR 1.30, 95% CI 1.14–1.49). The authors concluded that PPIs use was a marker, and not the cause, of a higher rate of CV events in the PLATO trial.

RECOMMENCING ANTIPLATELET THERAPY FOLLOWING BLEEDING

1. Aspirin should be recommenced early to reduce CV mortality although it increases the risk of GI bleeding

The decision to continue with antiplatelet therapy remains a clinical challenge, especially in those who need to continue

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their antiplatelet therapy due to a recent MI, and post-PCI with stent implantation. Obviously, the initial step is to assess whether antiplatelet therapy is still required. If there is a continuous need, then following endoscopic therapy for GI bleeding the endoscopist will have to decide if continuing antiplatelet therapy is possible. If hemostasis is achieved and the risk of rebleeding is low, then antiplatelet therapy could be resumed immediately. At present, there are no published data to recommend the ideal timing to restart antiplatelet therapy. In patients at high risk of recurrent bleeding, resuming antiplatelet therapy between days 3–5 is a reasonable approach, as most recurrent ulcer bleeding occur within 72 h and the half-life of antiplatelet agents is 5–7 days.

Adherence to aspirin in a non-acute situation was associated with a significant reduction in MI.[71] Similarly, Rodriguez *et al.*[72] confirmed that poor compliance with aspirin among patients with coronary heart disease was significantly associated with a higher rate of MI. In a meta-analysis Biondi-Zoccai *et al.*[73] revealed that aspirin non-adherence or withdrawal was associated with a threefold increase risk of major adverse cardiac events. This risk was even higher in patients with intracoronary stents (OR 89.78). In a randomized placebo-controlled trial, Sung *et al.*[74] assessed the risk of recurrent bleeding and CV mortality in patients who continue to receive aspirin with PPIs following endoscopic therapy to control peptic ulcer bleeding. Continuous aspirin therapy was associated with a higher risk of recurrent ulcer bleeding but lower mortality. Peptic ulcer healing was not affected by the continuation of aspirin once PPI is started. The peptic ulcer healing rate is similar in patients treated with PPIs alone or PPIs plus aspirin.[75]

In conclusion, antiplatelet drugs are the cornerstone in the management of CV diseases but they are associated with the risk of GI bleeding. A prior history of peptic ulcer bleeding or other complications are the strongest risk factors and predictors for the subsequent peptic ulcer bleeding. PPIs co-prescription in the highrisk group is associated with a reduced risk of GI bleeding in patients requiring antiplatelet therapy. Data on clopidogrel–PPI interactions are inconclusive and PPIs should be considered after balancing the CV risk and GI complications in patients treated with clopidogrel, especially in combination with aspirin and other risk factors. Newer antiplatelet agents are suitable alternatives, as they have not been shown to have any significant interactions with PPIs. The early commencement of antiplatelet agent following GI bleeding has been shown to reduce CV mortality, despite the risk of increases in recurrent bleeding.

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MSGH REPRESENTATION AT THE 12TH SEOUL INTERNATIONAL DIGESTIVE DISEASES SYMPOSIUM (SIDDS 2012)

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Professor of Medicine, UMMC
President Elect, MSGH

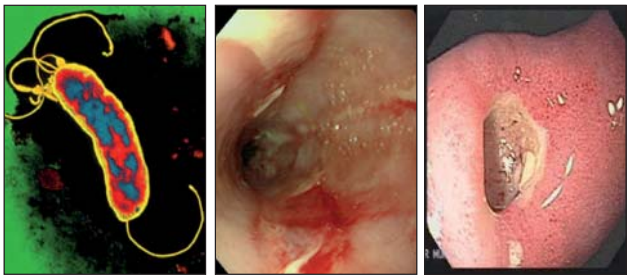
In 2012, the 12th Seoul International Digestive Diseases Symposium (SIDDS) was held in Seoul, Korea between November 23rd and 24th. The theme of the conference was "Asian Pacific Perspectives in Gastroenterology and Hepatology" and various Asian national Gastroenterology societies were invited to present clinical issues pertaining to Gastroenterological diseases in their respective countries. I had the honour of representing MSGH at this prestigious meeting and provided a brief glimpse of several GI diseases from Malaysia to an enthralled Korean audience. The article below represents the contents of the presentation and it has been published as an article in the SIDDS 2012 proceedings:

Gastroenterology Issues in Malaysia

INTRODUCTION

Malaysia, a rapidly developing nation situated in South East Asia, has a socio-demographically diverse population of almost 26 million people. A socio-economic divide exists between 40% of the population who reside in rural areas and amongst the remainder in cosmopolitan urban dwellings. The Malaysian population is additionally unique in its' multi-ethnic composition, with the Malays being the majority followed by the Chinese, Indians, Indigenous groups and Orang Asli. Thisdiversity, particularly with the various ethnic groups, has been particularly reflected in the epidemiology of gastrointestinal (GI) diseases in this country. This brief report of GI diseases in Malaysia will focus on some of the more common conditions affecting the population, namely Upper Gastrointestinal Diseases, Colorectal malignancy and Viral Hepatitis.

Upper Gastrointestinal Diseases



Like most other parts of Asia, *Helicobacter pylori* infection has been recognised as a major GI disease in Malaysia for some time. A large-scale population-based serological study, more than a decade ago, revealed a "racial cohort phenomenon" whereby significant differences in prevalence rates of *H. pylori* were observed among various ethnic groups[1]. Among 2381 adults from both East and West Malaysia, prevalence rates were highest among

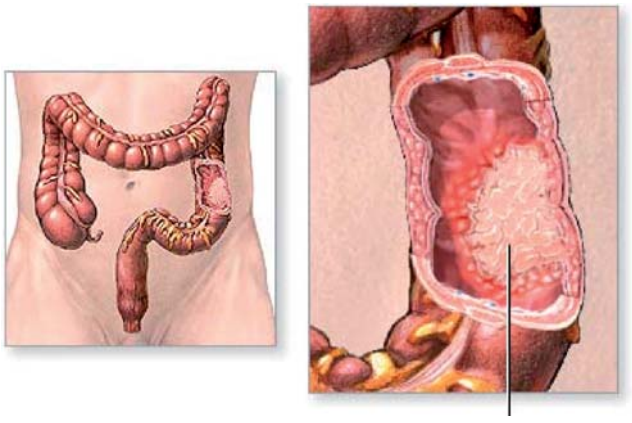
ethnic Chinese (26.7 - 57.5%) and Indians (49.4 - 52.3%), and lowest among ethnic Malays (11.9 to 29.2%). This difference in *H. pylori* prevalence appeared to partly correlate with a higher prevalence of peptic ulcer disease observed among non-Malay ethnic groups, compared to Malays, observed in an endoscopy-based evaluation of symptomatic adults with dyspepsia in 1997[2]. Lower rates of < 10% prevalence were additionally reported among ethnic Malay populations residing in mainly rural areas, with a corresponding low disease burden of peptic ulcer disease as well[3,4]. The differences in *H. pylori* prevalence, particularly between Malay and non-Malay ethnic groups, have been purported to be mainly due to "host" factors. Studies on the "virulence factors" of *H. pylori*, have revealed some differences in prevalence between the major ethnic groups with respect to cagA (Malay 76.6%, Chinese 86.4%, Indian 86.8%), cagE (Malay 70%, Chinese 39%, Indian 81.6%) and vacA (Malay 66.7%, Chinese 54.2%, Indian 76.3%) genetic strains, but these were insufficient to explain the clinical differences in upper GI disease among the ethnic groups[5].

With regard to treatment, several studies have been conducted on the optimal treatment for *H. pylori* in Malaysian patients. A standard therapy with proton pump inhibitor (PPI), amoxycillin and clarithromycin for a 1-week duration has been adopted widely as the treatment of choice with a good eradication rate for more than a decade[6]. Recently, this same triple therapy regimen was re-evaluated in a study of 191 patients and found to have a 84.4% eradication rate with a low side-effect rate[7]. Antibiotic susceptibility studies among Malaysian patients have demonstrated a fairly high Metronidazole resistance rate, ranging from 37% - 75%, but low Clarithromycin resistance[8,9], which would explain the continued high eradication rates with the standard Amoxycillin-Clarithromycin-PPI regime. Nevertheless, a recent study of *H. pylori* eradication failures (to first line therapy) has demonstrated that a second-line therapy with high dose Amoxycillin-PPI regime for 2 weeks and a third-line Amoxycillin-Levofloxacin-PPI 2 week regime was able to eradicate most patients with initial treatment failure[10].

Similar to various geographical regions in Asia, the prevalence of *H. pylori* and *H. pylori*-associated disease appears to have declined in Malaysia over the last few decades. A retrospective review of a single-centre's endoscopy reports from 1990 to 2000, i.e. over a decade, documented a decline of *H. pylori* prevalence from 51.7% to 30.3%, a reduction of duodenal ulcers from 21% to 9.5% and of gastric ulcers from 11.9% to 9.4%[11]. Although the incidence of peptic ulcer disease and *H. pylori* infection has been on the decline in Malaysia, a parallel increase in gastro-esophageal reflux disease (GERD), particularly among urban areas, has been observed[11]. No community-based studies on GERD have been conducted in Malaysia to date, but large endoscopy-based studies have suggested some interesting clinical and epidemiological observations. Erosive oesophagitis has been reported in as much as 10 - 15% of adults with symptoms, but most of these were of mild inflammation (Los Angeles Classification Grade A or B) and significantly more prevalent among ethnic Indians compared to non-Indians in urban areas[12,13]. Despite this notable increase in erosive GERD, a clinical study comparing Malaysian patients to an age-matched group of Caucasian patients from the U.K. showed a lower proportion of erosive GERD (5.8% *vs* 26.8%) and GERD symptoms among Malaysians[14].

Population-based studies in Malaysia have demonstrated important epidemiological observations in dyspepsia. An urban-based study reported a 24.3% prevalence of dyspepsia among 2039 adults, while demonstrating that Malay and Indian ethnicity were independent risk factors for the condition[15]. A lower prevalence of dyspepsia, at 14.6%, was subsequently reported in a rural survey of 2000 adults, whilst indicating that socioeconomic factors were associated with the presence of dyspepsia[16]. Although considered to be a benign condition, these community- based studies further demonstrated high rates in healthcare consultation behaviour for dyspepsia in both rural and urban areas[17], which eventually translated to a significant economic burden to both society and healthcare provider[18]. To try to reduce this economic burden of dyspepsia, a randomised trial of *H. pylori* "test and treat" *versus* prompt endoscopy was conducted and shown to be more cost-effective in the initial management of dyspepsia among young adults in Malaysia[19].

Colorectal Cancer



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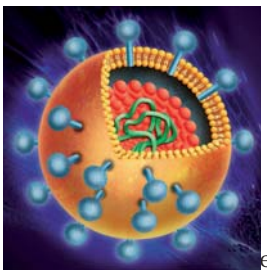
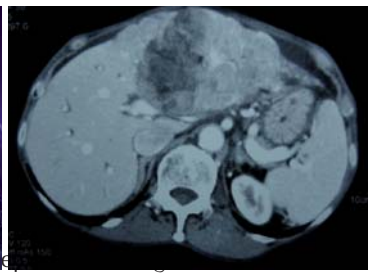
Colorectal cancer (CRC) has become the most common GI malignancy in Malaysia over the last decade, possibly associated with urbanised lifestyle and changes in dietary practices. The 2008 National Cancer Registry, which captured national data from the period of 2003 - 2005, reported that CRC was the commonest cancer among Malaysian men (14.5% of all cancers) and the third most common cancer for women (9.9% of all cancers)[20]. Epidemiologically, CRC had a significant rise in incidence after the age of 60 years, had a male to female ratio of 1.1: 1, and a higher incidence rate among ethnic Chinese compared to non-Chinese ethnic groups[20]. Although wide-spread screening for CRC has not been implemented yet, data from symptomatic patients undergoing colonoscopy have provided some clinical insight into the disease in Malaysians. A single-centre retrospective review of 228 cases of CRC revealed that 80% of tumors were located in the left hemi-colon, particularly in the recto-sigmoid junction[21].

Another retrospective review of 107 cases of CRC highlighted that many patients with CRC presented with symptoms of anemia or frank rectal bleeding, with a median symptom duration of 13 weeks[22]. Due to the delay in presentation among many patients, an advanced stage of CRC is usually observed at initial presentation, with Duke's C stage disease present in 40%[22] or more[21] of patients. In view of the poor awareness among the public at large, it has also been reported that adults from a lower socioeconomic background, particularly those from rural areas have a poorer long-term outcome due to prolonged symptoms and delayed presentation[23]. The delayed clinical presentation of patients, together with a further delay of medical investigation procedures in over-burdened public healthcare institutions, have also been identified as poor prognostic factors for eventual outcome of CRC among Malaysian patients[24]. It is generally accepted that CRC screening in an asymptomatic at risk population would yield a better overall outcome for the disease in Malaysia. However, several barriers to the implementation and acceptance (by the public) of this process need to be overcome before it can be practiced successfully[25].

Viral Hepatitis





healthcare services in Malaysia, particularly in the form of decompensated cirrhosis[26 27]. The commonest aetiology of chronic liver disease in Malaysia, as it is in most parts of the Asia Pacific region, is that of Hepatitis B and to a lesser extent, Hepatitis C, infection. Data from almost two decades ago revealed that the HBsAg carrier rate among "healthy adults" ranged from 1 - 10% 28. Based on blood donor statistics then, the frequency of HBsAg positivity was highest among ethnic Chinese (4-7%), followed by Malays (2 - 4%) and lowest among Indians (< 1%)[28]. Hepatitis B then had a male preponderance with a male: female ratio of 2-3:1. Approximately 35% of adults infected had HBeAg antigenemia, and half of these patients had elevated liver function tests.

As the major mode of transmission of Hepatitis B in this region is mainly through a vertical / perinatal route, serological surveys two decades ago reported HBsAg carrier rates of up to 10% in Malaysian pregnant women, depending on ethnic groups studied[29]. Although vaccination for HBsAg carrier had been initiated in the 1980s in Malaysia, an expanded programme of immunisation had later been implemented in the 1990s for children of school-going ages. A study published in 2005 was able to demonstrate that this programme in Malaysia resulted in a steady decline of HBV surface antigen (HBsAg) prevalence rate from 2.5% for children born in 1985 to 0.4% among school children born in 1996[30]. A study in a Northern Malaysian state in 2008 reported that the HBsAg carrier state among pregnant women had declined to 1.45%[31]. Whilst the epidemiology of Hepatitis B infection in Malaysia is generally understood, details on the clinical management of our patients and response rates to current anti-viral therapy remain lacking. Further data on response to therapy and its' impact on the outcome of Malaysian patients with Hepatitis B is urgently required.

In contrast to Hepatitis B, Hepatitis C infection has been reported to have a significantly lower prevalence among Malaysians. Several studies among potential blood donors in urban areas have previously reported prevalence rates ranging from 1.5%[32] to 3%, with no differences among various ethnic groups nor across gender[33]. However, due to its high parenteral transmission affinity and lack of awareness of its' presence before nation-wide screening, several at-risk groups of patients have developed high rates of infection. A serological study in 1993 demonstrated very high rates of HCV antibody levels among intravenous drug users (85.3%), hemophiliacs (64.3%) and renal failure patients on regular hemodialysis

(53.9%) compared to various other groups of individuals such as healthcare workers (0%) and homosexuals (10.8%)[33]. A recent study of intravenous drug users across several urban areas in Malaysia reported an overall HCV infectivity rate of 67.1%, indicating that this group of patients remains at risk of the well recognised complications of HCV infection.

The commonest genotype of Hepatitis C in Malaysia is believed to be that of genotype 2 and 3. As a result, reasonable sustained viralogical response (SVR) rates have been reported with standard therapy in the form of pegylated interferon α-2a or α-2b and ribavirin. A single-centre in Northern Malaysia reported SVR rates of 60% following standard treatment for 33 patients across various HCV genotypes[34]. Even in difficult-to-treat groups such as those with end stage renal failure, SVR rates of 50% have been reported in another Malaysian study using a gradual increment of pegylated interferon α-2b doses[35]. Whilst the early reports of treatment of HCV patients are encouraging, further studies examining access to treatment for socially segregated members of society and their long-term impact are also needed.

CONCLUSION

This brief report on several issues of some common GI diseases in Malaysia is by no means exhaustive. Nevertheless, the unique demographics of the Malaysian population offers an opportunity to study important epidemiological aspects of GI diseases, which are also relevant to other parts of Asia.

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MULTIPLE DISCIPLINARY APPROACH TO MANAGING LIVER METASTASES FROM COLORECTAL CANCER

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Colorectal cancer: Scope of the problem

Colorectal cancer is the third commonest cancer worldwide after lung and breast cancer, according to the World Health Organization (WHO) in 2012. It is the fourth leading cause of caner-related death. In Asia, many countries, including China, Japan, South Korea, and Singapore, have experienced a two- to fourfold increase in the incidence in the past two decades. In Malaysia, the annual incidence of colorectal cancer is reported to be 17.5 per 100,000 patient population. With our national population estimated at 29 millions, approximately 5075 new cases of colorectal cancer are expected to be diagnosed each year.

Approximately fifty percent of the colorectal cancer will eventually metastasize to the liver, either in synchronous (at the same time of diagnosis or within 6 months) or metachronous presentation. Liver is the only site of metastasis in 30-40% of the colorectal cancer. This is termed stage IV disease and if left untreated, the prognosis is extremely poor with survival between 6-12 months.

Liver resection vs. chemotherapy vs. RFA

With recent improvement in the fields of surgical and medical oncology, long-term survival,or even cure - in patients with colorectal cancer and liver metastasis - is no longer an elusive dream! With a combination of chemotherapy and liver resection, 5-year survival rates range from 40-60%, and 10-year survival rates of 25-28% can be expected - a remarkable achievement in stage IV disease. The largest international database (livermetsurvey.org) reported 5-year survival rate of 42% and 10-year survival rate of 26% in 16,779 patients recorded from 63 countries. This excellent result is achievable only with R0 liver resection (complete tumour excision). In comparison, most palliative chemotherapy regimes offer survival rates of only 2% in 5 years and no long-term survival. Themo-abaltion with radio-frequency (RFA) offers inferior survival rate compared with surgical resection. [Figure 1] It is clear from existing literature that liver resection makes a difference in improving survival and is now considered the gold standard of treatment.

Multi-disciplinary Management of Colorectal Liver Metastases

When patients present with colorectal cancer with liver metastases, achieving long-term survival and cure is still possible if optimal management can be started under the auspices of multi-disciplinary management. Members of the multi-disciplinary team consist of colorectal surgeons, clinical oncologists, interventional radiologists, gastroenterologists, and liver surgeons. Since the combinations and permutations of different treatment modalities are numerous, it is better to discuss all new cases of colorectal cancer involving all interested parties from the outset. For example, obstructing colon cancer will require urgent colectomy with delay chemotherapy and liver resection. On the other hand, systemic chemotherapy may be started first if the patient has to undergo long-course radiotherapy for low rectal cancer

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and liver-dominant disease. Timely intervention of liver surgeon also requires careful coordination with the oncologist and colorectal surgeon if simultaneous resection of colorectal cancer and liver metastases is contemplated. Rather than involving different sub-specialties midway through the treatment in a haphazardly organized fashion, MDT plots the individualized treatment course right from the outset in a coordinated fashion.

MDT management of cancers is nothing new; most developed nations have introduced such management and have demonstrated improved cancer care and survival over the past decades. The United Kingdom, for example, has made discussion of all, newly diagnosed cancer cases compulsory-by-law in the MDT setting before any treatment can be started.In Malaysia, MDT is still not widely practiced and there is room for improvement.

Synchronous Colorectal Liver Metastases

When patients present with synchronous colorectal liver metastases, it is useful to sub-categorize the presentations into three categories in planning for the management: Group 1 - unresectable liver metastases with a resectable primary colorectal tumour; Group 2 -resectable liver metastases and colorectal tumour; and finally Group 3 - marginally resectable liver metastases with resectable primary colorectal tumour.

Unresectable colorectal liver metastases

Ninety percent of the newly diagnosed colorectal liver metastases were found to be unresectable initially. If the liver metastasis is unresectable, resection of the primary colorectal tumour offers no survival benefit. Resection of the primary tumour is only justified in the presence of perforation, impending obstruction or profuse bleeding; otherwise, systemic palliative chemotherapy should be started as soon as possible. By performing colectomy first, not only does the survival rate not improved, the risk of disease progression during the post-operative period is high. Furthermore, surgical complications may cause further delay in starting chemotherapy, and the chance of early disease control is lost. Partially obstructed colorectal cancer may be palliated with metallic stent and bleeding rectal tumour may be arrested by radiotherapy. The majority of patients with minor symptoms will respond to the chemotherapy with marked symptomatic improvement. Only approximately 10% of the patients who undergoes chemotherapy will require surgical intervention during treatment, either because of tumour obstruction, perforation, or profuse bleeding.

Resectable Colorectal Liver Metastasis

Only 10-20% of the patients with synchronous colorectal liver metastases are found to be resectable at the time of diagnosis. Traditionally, the colorectal surgeon will resect the primary tumour first; after a recovery period of up to one month, the patient undergoes liver resection. Systemic adjuvant chemotherapy is usually started either after the colorectal surgery or after the liver surgery.

With recent improvement in anaesthetic techniques and surgical skills, simultaneous resection of the colorectal tumour and liver metastases can be undertaken during a single operation. This is a popular choice with the patients because of one operation risk and one post-operative recovery, shorter duration of recovery, and lower cost. The disadvantages are higher anaesthetic risks because of the longer duration, and the summative effects of the surgical risks. At present, only minor hepatectomy (wedge resection lasting 1-2 hours) is considered suitable for simultaneous resection. Staged resection (colon first, liver later) should be considered if patients have significant comorbidities, or if extensive resection is considered (eg. major hepatectomy or low anterior resection). The choice of giving chemotherapy in the neo-adjuvant (pre liver resection) or adjuvant (post liver resection) settings remains controversial. In the absence of definitive data, discussion with the oncologist within the context of MDT is encouraged.

Marginally Resectable Colorectal Liver Metastases

Ninety percent of the colorectal liver metastases are found to be unresectable at presentation. However, within this group, some 20-30% of patients with initially unresectable liver metastases may be converted into resectabledisease by the use of optimal chemotherapy. Studies have demonstrated that if chemotherapy can downstage the liver metastases, the long-term survival is similar to the liver resection group. This is where the MDT decision-making from the outset is most critical in determining the fate of the patients. With collaboration of the oncologist and liver surgeon, individualized treatment

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course can be planned from the outset to ensure optimal treatment.

Currently, it is a common practice for the non-liver surgeons (oncologists, colorectal surgeons, or even gastroenterologists) to determine the resectability of the liver metastases based on the CT scan reports; as a result, the liver resection rate is low and the patients suffer poor outcome. Recent improvement in surgical skills has led many liver surgeons to expand the criteria of resectability, and the traditional resectability criteria can no longer be applied. The goal of liver surgery is to achieve a R0 resection with microscopic clear surgical margins. New surgical techniques, such as portal vein embolization, parenchymal-sparing liver resection, two-staged heaptetomy, and combination of resection and RFA, have expanded the armamentarium of surgeons resecting liver metastases. As a general rule, up to 70-75% of the liver parenchyma can be resected, provided that the remnant liver has adequate blood supply and bile drainage. Within a month, the remaining liver will regenerate and undergo hypertrophy to a size close to the pre-resection liver volume. Therefore, liver surgeons must be involved in the decision making of resectability from the outset.

For the marginally resectable disease, optimal chemotherapy should be given in an attempt to downstage the disease. After the fourth cycles of chemotherapy, typically after 6-8 weeks of treatment, CT scans should be repeated to determine resectability. If insufficient response is obtained, the oncologist should consider a change of chemotherapy regime. The more lines of chemotherapy regime, the lower the chance of inducing resectability. Therefore, it is important to use the most powerful chemotherapy regime first in order to achieve a good response. Too long a course of chemotherapy (>6 cycles) would also render liver surgery hazardous because of the risk of hepato-toxicities. Chemotherapy-induced steatohepatitis or sinusoidal obstructive syndrome will result in increased risks of bleeding, liver failure, and bile leak during the peri-operative period. Therefore, a short duration of chemotherapy (<6 cycles) is ideal if liver surgery is contemplated. With optimal chemotherapy, some 20-30% of the initially unresectable liver metastases can be "rescued" and converted into resectable disease with far superior long-term survival. Coordination and cooperation between oncologist and liver surgeon is a perquisite in achieving this goal.

Conclusion

Recent improvement in medical and surgical oncology has resulted in marked improvement of survival in patients with colorectal liver metastases. Liver surgery, if possible, offers the best long-term survival and the opportunity to be cured. Liver surgeons must involve in determining the resectability of liver metastases from the outset. Multi-disciplinary approach to the management of colorectal liver metastases will improve survival. MSGH

Figure 1: Survival rates of different modalities in colorectal liver metastases. Liver surgery offers the best survival rate.