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**EDARBYCLOR** – the first and only ARB fixed-dose combination with chlorthalidone

- **EDARBYCLOR** is the first and only ARB/chlorthalidone combination
- **EDARBYCLOR** demonstrated superior systolic BP reduction vs olmesartan HCTZ²
- Chlorthalidone is superior at preventing cardiovascular events compared to amloidipine besylate³

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**HYPERTENSION: WHEN IT IS DIFFICULT TO TREAT**

<table>
<thead>
<tr>
<th>Reduction in clinic SBP/DBP with EDARBYCLOR at week 8'</th>
<th>EDARBYCLOR 40/12.5 mg</th>
<th>EDARBYCLOR 40/25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline: 165/96 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td>-36.8 mmHg</td>
<td>-39.5 mmHg</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td>-15.6 mmHg</td>
<td>-17.0 mmHg</td>
</tr>
</tbody>
</table>

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For detailed information, please consult full prescribing information.


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Takeda Pharmaceuticals (HK) Ltd.
23/F & 24/F, East Exchange Tower, 38 Leighton Road, Causeway Bay, Hong Kong
Tel 2133 9400 / Fax 2856 2728 / www.takeda.com
Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) have become established as a popular treatment for hypertension due to their ability to reduce blood pressure (BP) effectively and their excellent tolerability profile. They are recommended as potential first-line antihypertensive treatments in the most recent guidelines from the United States and Europe.1,2

Whilst ARBs have generally performed well in comparison with placebo and some other drugs, comparisons with angiotensin converting enzyme (ACE) inhibitors have not always been favourable for ARBs. In a meta-analysis of studies in patients at high cardiovascular (CV) risk without heart failure (HF), both ACE inhibitors and ARBs reduced the risk of the composite outcome of CV death, myocardial infarction (MI), and stroke, but only ACE inhibitors significantly reduced the risk of all-cause death, new-onset HF, and new-onset diabetes mellitus (DM) in the studies included in the analysis.3 In another recent meta-analysis of studies in patients with DM, it was found that ACE inhibitors reduced all-cause mortality, CV mortality and major CV events, whereas ARBs had no significant benefits on these outcomes.4 However, the only large trial that directly compared ARB and ACE inhibitor – the ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study – showed that telmisartan had similar benefits to ramipril on vascular events and major renal outcomes, though telmisartan was better tolerated.5 The ONTARGET study also showed that the combination of ARB and ACE inhibitor was associated with more adverse events without an increase in benefit. In view of this and data from other studies, it is generally not recommended to use a combination of these two types of drugs to block the renin-angiotensin system.

All ARBs are generally well tolerated, but they can differ in their pharmacokinetic properties and approved indications (Table 1). They may also differ in their

<table>
<thead>
<tr>
<th>Drug</th>
<th>Losartan (E3174)</th>
<th>Valsartan</th>
<th>Irbesartan</th>
<th>Candesartan</th>
<th>Cilexetil</th>
<th>Telmisartan</th>
<th>Eprosartan</th>
<th>Olmesartan medoxomil</th>
<th>Azilsartan medoxomil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>33</td>
<td>10–35</td>
<td>60–80</td>
<td>15</td>
<td>40–60</td>
<td>13</td>
<td>26–29</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>1–3 (6–9)</td>
<td>6–9</td>
<td>11–15</td>
<td>5–9</td>
<td>20–38</td>
<td>20</td>
<td>10–15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution (L)</td>
<td>34 (12)</td>
<td>17</td>
<td>53–93</td>
<td>0.13 L/kg</td>
<td>500</td>
<td>308</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Usual daily dose (mg)</td>
<td>50–100</td>
<td>80–320</td>
<td>150–300</td>
<td>8–32</td>
<td>40–80</td>
<td>400–800</td>
<td>20–40</td>
<td>40–80</td>
<td></td>
</tr>
<tr>
<td>Approved indications</td>
<td>HT, diabetic nephropathy, reduction of risk of stroke in HT with LVH</td>
<td>HT, heart failure, reduction of CV mortality in clinically stable patients with LVF or LVD following MI</td>
<td>HT, diabetic nephropathy</td>
<td>HT, heart failure</td>
<td>HT, reduction of high CV risk</td>
<td>HT</td>
<td>HT</td>
<td>HT</td>
<td></td>
</tr>
</tbody>
</table>

CV, cardiovascular; E3174, active metabolite of losartan; HT, hypertension; LVD, left ventricular dysfunction; LVF, left ventricular failure; LVH, left ventricular hypertrophy; MI, myocardial infarction.

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Key words: Hypertension (高血壓), angiotensin receptor blockers (血管緊張素受體拮抗劑), azilsartan (阿齊沙坦)
antihypertensive efficacy as shown in a meta-analysis of ARBs as monotherapy. Based on the ambulatory BP monitoring (ABPM), ARBs had a shallow dose-response curve. Uptitration only marginally enhanced the antihypertensive efficacy and BP reduction with losartan over the dose range was consistently inferior to that with other ARBs. In an earlier systematic review of antihypertensive activity of the seven ARBs based on 24-hour ABPM, olmesartan showed the greatest BP reductions over 24 hours. Olmesartan-based treatment also proved very effective in lowering BP in diabetic patients in the ROADMAP trial. The study also showed that despite the significantly delayed onset of microalbuminuria, there was a higher rate of fatal CV events with olmesartan, particularly among patients with pre-existing coronary heart disease. This may have been related to excessive BP lowering in these patients and this finding highlights the importance of a cautious approach to BP reduction in patients with known coronary ischaemia.

One meta-analysis of randomized controlled trials also concluded that ARBs are associated with a modestly increased risk of new cancer diagnosis, but this was refuted by subsequent meta-analyses.

### Azilsartan medoxomil

Azilsartan medoxomil (TAK-536, Edarbi®) is the most recently introduced ARB. It has been approved in the United States, Europe and several other countries, including Hong Kong, for the treatment of hypertension. Azilsartan medoxomil is a prodrug that is rapidly and completely hydrolyzed to its active compound, azilsartan, in the gastrointestinal tract and/or during drug absorption. Azilsartan has a unique 5-oxo-1,2,4-oxadiazole moiety in place of the tetrazole ring which is present in most other ARBs (Figure 1). Peak plasma concentrations of azilsartan are reached 1.5 to 3 hours after administration. The oral absorption of azilsartan medoxomil is not influenced by the presence of food, and the bioavailability based on plasma azilsartan concentrations is about 60%. The elimination half-life is about 12 hours, thus allowing once-daily dosing. Azilsartan undergoes cytochrome P450 (CYP) 2C9-mediated decarboxylation to form metabolite M-I, and O-dealkylation to produce metabolite M-II, and both of these metabolites are inactive. Approximately 55% of the drug is eliminated in the faeces, 42% in the urine, and 15% as unchanged azilsartan.

Studies on the binding affinities of azilsartan for the angiotensin II type 1 [AT1] receptor and the inverse agonist activity toward the production of inositol phosphate showed that both azilsartan and candesartan interact with the same three sites in the AT1 receptor. However, the hydrogen bonding between the oxadiazole of azilsartan and the Gln257 site on the AT1 receptor is stronger than that between the tetrazole of candesartan and the Gln257 site. Stronger interaction with the Gln257 site was shown to induce greater inverse agonism. An earlier study showed that candesartan interacts with four sites in the AT1 receptor and this also appears to be the case for azilsartan. In vitro studies comparing the inhibitory effects of azilsartan versus other ARBs on contractile responses induced by angiotensin II demonstrated that azilsartan conferred persistent inhibition after washout, with greater potency compared with olmesartan. These findings suggested that azilsartan is a highly potent and slowly dissociating ARB, and the tight receptor binding might be expected to produce potent and long-lasting antihypertensive effects.

The usual starting dose of azilsartan medoxomil is 40 mg once daily but a starting dose of 20 mg should be considered in elderly patients (≥75 years) and those with mild-to-moderate hepatic impairment or intravascular volume depletion.

The BP lowering effect of azilsartan medoxomil has been examined in seven double-blind controlled studies in a range of patients. In two studies comparing azilsartan medoxomil with placebo, the reductions in trough clinic systolic BP after six weeks of treatment were 14.5 and 16.4 mm Hg with azilsartan medoxomil 40 mg, and 176 and 16.7 mm Hg with azilsartan medoxomil 80 mg, compared with 2.1 and 1.8 mm Hg with placebo. Notably, azilsartan medoxomil resulted in significantly greater reductions in systolic BP when compared with the highest approved doses of olmesartan medoxomil and valsartan. Azilsartan medoxomil was generally well tolerated, with a tolerability profile similar to that of placebo in 6-week trials.

Combination therapy is required in the majority of patients with hypertension. The combination of azilsartan medoxomil with chlorothalidone provided better BP reduction and a higher likelihood of achieving BP control compared with the combination with hydrochlorothiazide. Combined tablets of azilsartan medoxomil 40 mg with chlorothalidone 12.5 mg or 25 mg are currently available.

Like other ARBs, azilsartan has few major drug interactions. In addition...
to increasing serum lithium concentrations, its concomitant use with non-steroidal anti-inflammatory drugs or selective cyclooxygenase-2 inhibitors may reduce the antihypertensive effect of azilsartan and can worsen renal function and cause hyperkalaemia. Concomitant use of potassium-sparing diuretics or other drugs that may increase potassium levels can also increase the risk of hyperkalaemia. As with other ARBs, azilsartan medoxomil should be avoided in pregnant women and in patients with bilateral renal artery stenosis.

The pleiotropic effects attributed to azilsartan include antithrombotic, anti-proliferative and potentially antifibrotic effects. Beneficial effects on insulin sensitivity and glucose metabolism, improved endothelial function, and antiproteinuric effects have also been observed. Whether or not these will improve endothelial function, and sensitivity and glucose metabolism, rollefrative and potentially antifibrotic effects have also been observed. Whether or not these will improve endothelial function, and sensitivity and glucose metabolism, rollefrative and potentially antifibrotic effects have also been observed. Whether or not these will improve endothelial function, and sensitivity and glucose metabolism, rollefrative and potentially antifibrotic effects have also been observed. Whether or not these will improve endothelial function, and sensitivity and glucose metabolism, rollefrative and potentially antifibrotic effects have also been observed.

Conclusion

ARBs have proven to be effective in lowering BP and in reducing certain CV outcome events. Azilsartan medoxomil is the most recent ARB to be approved for the treatment of hypertension and it appears to be more effective in reducing BP than any of the other ARBs. The improved BP lowering efficacy may be related to features of it’s chemical structure, which increase the binding of the drug to the AT1 receptor. The powerful antihypertensive effect and excellent tolerability profile support azilsartan medoxomil as an attractive treatment option for patients with hypertension, although additional studies are needed to examine the effects of azilsartan medoxomil on cardiovascular outcomes.

References


THE SOCIETY OF PHYSICIANS OF HONG KONG

CME Lecture July 11, 2014 (Friday) Free admission for doctors

Topic: Updates in Breast Cancer Treatment

Speaker: Dr Ma Tin Wei, Ada (馬天慧醫生 ) MBChB (CUHK), MRCP (UK), FRCP (Edin), FRCP(Glasg), FHKCP, FHKAM(Medicine)
Specialist in Medical Oncology

Sponsor: Hospira Limited.

Place: HKMA Dr Li Shu Fui Professional Education Centre
2/F, Chinese Club Building, 21–22 Connaught Road Central, HK

Time: 1:15 pm Lunch 2:00–3:00 pm Lecture

On first come first serve basis. No confirmation will be sent for registration. Pre-registration is required. Unsuccessful applicants will be informed.

Registration form: Fax to 3588 2479 Enquiry: 2526 2626

Web registration and further details: www.SOPHYSICIANSHK.org

I wish to attend meeting and lunch on July 11, 2014 (Free admission)

Name of doctor (surname first):______________________________ Tel:______________
Personalized Treatments for Metastatic Colorectal Cancer

O
ver recent years, diet and lifestyles have changed considerably with an increase in the consumption of red meat and saturated fat. Consequently, the incidence of metastatic colorectal cancer (mCRC) in Hong Kong has risen significantly. Smoking and alcohol consumption have also been shown to increase the likelihood of developing this type of cancer. Figures from the Hong Kong Cancer Registry show that since 2011 colorectal cancer has eclipsed lung cancer as the most prevalent cancer in Hong Kong, with 4,450 incidences and over 1,900 deaths reported in 2011 alone.\(^1\)

Only 8.8% of patients with colorectal cancer are diagnosed at stage I, and at this early stage the 5-year observed survival rate is 74%. Patients with stage IV disease comprise almost a quarter of all newly diagnosed colorectal cancer cases and at this stage the 5-year survival rate drops markedly to 6%.

Currently there are two types of treatment options available to patients with mCRC:

1. Chemotherapy - using oxaliplatin or irinotecan with oral or infusional fluoropyrimidine.
   a. Studies have shown a comparable efficacy between using oxaliplatin-based chemotherapy (FOLFOX) or irinotecan-based chemotherapy (FOLFIRI).\(^2\)

2. Target therapy - using either anti-vascular endothelial growth factor (VEGF), bevacizumab, or anti-epidermal growth factor receptors (EGFR), cetuximab and panitumumab, in combination with chemotherapy.
   a. Anti-VEGF treatment inhibits the binding of VEGF to its receptors on the surface of endothelial cells; thereby inhibiting angiogenesis and vascular permeability of the tumour.
   b. Anti-EGFR treatment works by blocking EGF ligand binding and stimulating receptor degradation, which leads to prevention of EGFR-associated signaling resulting in tumour shrinkage.

It is important to understand that target therapy must be personalized. All patients with mCRC should be tested for biomarkers, i.e. KRAS and NRAS mutation status (RAS mutation status) of the tumours. RAS mutations are crucially important as anti-EGFR treatment is only beneficial for patients with wild-type RAS mCRC. A meta-analysis of OPUS (phase II) and CRYSTAL (phase III) trials documented that overall survival was increased with the addition of cetuximab to FOLFOX or FOLFIRI in patients with wild-type RAS (Figure 1).\(^3\)

Key words:
Personalized treatments (個人化治療), metastatic colorectal cancer (擴散性大腸癌), RAS biomarker testing (RAS生物標記測試), chemotherapy (化療), target therapy (標靶治療), cetuximab (西妥昔單抗)

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**Figure 1. Current treatment paradigm in metastatic colorectal cancer**

![Figure 1](image_url)

- **Metastatic colorectal cancer (mCRC) diagnosed**
  - **RAS biomarker testing**
    - **RAS wild-type**
      - **Anti-EGFR + chemotherapy**
    - **RAS mutant**
      - **Anti-VEGF + chemotherapy**
  - **1st line treatment**
FIRE-3, a phase III, randomized, open-label, multicentre trial, is the first head-to-head study to compare cetuximab and bevacizumab in combination with FOLIFIRI as first-line treatment for patients with wild-type RAS mCRC. The trial results demonstrated a longer overall survival for patients receiving anti-EGFR treatment rather than anti-VEGF. Those patients receiving cetuximab-based treatment survived an average of 33.1 months compared with 25.6 months for those patients receiving bevacizumab-based treatment (Figure 2).

Currently there are two anti-EGFRs available, cetuximab and panitumumab. However, they have different molecular structures, which lead to differences in their anti-tumor effects and toxicity profile. Cetuximab, an IgG1 subtype antibody, makes use of the patients’ antibody-dependent cellular cytotoxicity (ADCC), to kill cancer cells. Panitumumab, an IgG2 antibody, does not activate ADCC and thus has a lower efficacy in treating mCRC. In the PRIME study, panitumumab treatment lead to increased skin and gastrointestinal toxicities because of the over-binding to EGFR in the skin, gastrointestinal mucosa and kidney.

In conclusion, personalized treatment for mCRC should be biomarker driven. For patients with wild-type RAS mCRC first-line treatment with cetuximab should be considered as it promotes longer patient survival with better quality of life.

A complete list of references can be downloaded from www.SOPHYSICIANSHK.org

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**Figure 2. Kaplan-Meier curves for overall survival according to treatment in the FIRE3 trial**

- **Cetuximab + FOLFIRI**
  - Events: 91/171 (53.2%)
  - Median (months): 33.1
  - 95% CI: 24.5-39.4
  - HR 0.70 (95% CI: 0.53-0.92)
  - p (log-rank)=0.011

- **Bevacizumab + FOLFIRI**
  - Events: 110/171 (64.3%)
  - Median (months): 25.6
  - 95% CI: 22.7-28.8

Δ = 7.5 months
Colorectal cancer (CRC) has become the most common form of cancer and the second leading cause of cancer death in Hong Kong. There were 4,450 new cases of CRC in 2011 with an overall upward trend for the age-standardized incidence rate for both sexes. There were 1,903 deaths caused by CRC in 2012. As most CRC arises from premalignant colonic polyps, and such polyps may take more than 10 years to progress into cancer, regular screening of the colon for colorectal polyp disease and cancer is an effective way to reduce the incidence and mortality of CRC.

Two important large scale long-term follow-up studies published recently have confirmed the benefit of colorectal screening and polypectomy. In the National Polyp Study, patients who underwent polypectomy between 1980 and 1990 were prospectively followed for up to 23 years. When compared with the expected mortality from CRC in the general population, those who had an adenoma removed during initial colonoscopy had a lower mortality rate from CRC (standardized incidence-based mortality ratio 0.47; 95% CI, 0.26–0.8), accounting for a 53% mortality reduction.

In another population-based case-control study from Germany, the risk of CRC was reduced by almost 90% up to 10 years after a colonoscopy, independent of the initial indications. The effect was even stronger for screening indication (adjusted odds ratio 0.09; 95% CI, 0.07–0.13) than other indications (such as positive faecal occult blood tests, abdominal pain, or surveillance after a preceding polypectomy). In this study, the right side colon cancer risk was reduced almost 80% after prior colonoscopy.

Who should be screened?
In 2008 the American Cancer Society, Multi-Society Task Force on CRC, and the American College of Radiology (ACS-MSTF-ACR) joint guidelines recommended that screening should be offered to asymptomatic average-risk individuals aged ≥50 years. This population accounts for 70–75% of patients with CRC. People with prior polyp disease, personal or family history of CRC, and underlying genetic mutations are classified as increased or high risk and screening schedules should be individualized.

To further stratify the risk of having colorectal advanced neoplasia (defined as any adenoma ≥10 mm in diameter, or with villous histology, or high grade dysplasia), especially in asymptomatic Asian subjects, The Asia-Pacific Working Group on Colorectal Cancer had validated four important risk factors. Subjects are classified in average-risk (0–1 point), moderate-risk (2–3 points) and high-risk (4–7 points) groups. Those in high- and moderate-risk groups have a higher chance of advanced neoplasia found during colonoscopy (compared with the average-risk group, relative risk 4.3 and 2.6). If resource is limited, those in the high-risk group should be prioritized for screening.

Other emerging risk factors include underlying coronary artery disease (CAD) and non-alcoholic steatohepatitis (NASH). In one local study, the prevalence of advanced neoplasm in CAD patients was 18.4%, compared with 5.8% in general population. In another local study, patients with biopsy-proven NASH had a higher prevalence of advanced neoplasm (34.7%) than controls (5.5%).

How to screen
To be a useful screening test for CRC, the test should be easy-to-use, safe and preferably non-invasive. The procedure and preparation should be acceptable to the screened subject. It should have a high sensitivity and acceptable specificity. It should also be low cost and affordable. Current screening methods have their intrinsic limitations. Therefore, despite

**Introduction**

Colorectal cancer (CRC) has become the most common form of cancer and the second leading cause of cancer death in Hong Kong. There were 4,450 new cases of CRC in 2011 with an overall upward trend for the age-standardized incidence rate for both sexes. There were 1,903 deaths caused by CRC in 2012. As most CRC arises from premalignant colonic polyps, and such polyps may take more than 10 years to progress into cancer, regular screening of the colon for colorectal polyp disease and cancer is an effective way to reduce the incidence and mortality of CRC.

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### Table 1. Asia Pacific colorectal screening score for prediction of risk for colorectal advanced neoplasia

<table>
<thead>
<tr>
<th>Age</th>
<th>0</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–69</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥70 years</td>
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<table>
<thead>
<tr>
<th>Gender</th>
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<tr>
<td>Female</td>
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<tr>
<td>Male</td>
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<table>
<thead>
<tr>
<th>Family history of CRC in a first degree relative</th>
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</thead>
<tbody>
<tr>
<td>Absent</td>
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<tr>
<td>Present</td>
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<table>
<thead>
<tr>
<th>Smoking</th>
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<tbody>
<tr>
<td>Never</td>
<td></td>
<td></td>
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<tr>
<td>Current or past</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Key words:**

Colorectal cancer, screening

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**Journal of The Society of Physicians of Hong Kong**

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**JUNE 2014**
widely advocating CRC screening, the participation is still low among average-risk adults, 29.8–55.2% in USA, and around 27% (range 1.5–69%) in Asia Pacific region.8,9

Screening methods

Table 2 summarizes the efficacy of currently used screening methods.10,11

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>One-time sensitivity for CRC</th>
<th>One-time sensitivity for advanced adenoma</th>
<th>Incidence reduction</th>
<th>Mortality reduction</th>
<th>Screening interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool-based tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gFOBT</td>
<td>13–75%</td>
<td>11–25%</td>
<td>18%</td>
<td>15–33%</td>
<td>Annual</td>
</tr>
<tr>
<td>FIT</td>
<td>60–85%</td>
<td>20–50%</td>
<td>—</td>
<td>—</td>
<td>Annual / Biennial</td>
</tr>
<tr>
<td>Stool DNA</td>
<td>80% +</td>
<td>40%</td>
<td>—</td>
<td>—</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Structural examination of colon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC</td>
<td>&gt;90%</td>
<td>90%</td>
<td>—</td>
<td>—</td>
<td>5 years</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>&gt;95% distal colon</td>
<td>30–70%</td>
<td>21%21</td>
<td>60% distal colon</td>
<td>5 years</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>95%</td>
<td>88–98%</td>
<td>53–90%</td>
<td>53%2</td>
<td>10 years</td>
</tr>
</tbody>
</table>

Table 2. Summary of the efficacy of currently using screening methods10,11

gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test; CTC, computed tomography colonography

Stool-based tests

Stool-based tests have the highest participation rates in screening programmes. However, their efficacy is limited by the relatively low sensitivity and specificity and repeat testing is needed. The traditional guaiac faecal occult blood test (gFOBT) has low sensitivity and need multiple stool samples. The new faecal immunochemical test (FIT) uses antibodies specific to human haemoglobin, albumin or other blood components and is more specific for human blood. By using a quantitative test, the sensitivity for advanced neoplasia (including cancers) is as high as 67%.13 A one-time stool sample could achieve better sensitivity and specificity than gFOBT and may be more acceptable to the patient.13 In a local screening programme involving over 10,000 subjects, the compliance rate with yearly FIT was 97.3%, 82.8%, 84.6% and 77.7% over consecutive 4 years.14 Despite FIT being more expensive than gFOBT, yearly FIT is more cost-effective in screening for both advanced neoplasia and CRC than a direct colonoscopy. Using FIT as a control, the incremental cost-effectiveness ratio (iCER) of screening colonoscopy was US$ 3,721, US$ 29,847 and US$ 984,120 to detect one adenoma, advanced neoplasm and CRC, respectively.14

In a large prospective study in Taiwan involving 18,296 subjects using one-time FIT for screening, the sensitivities for non-advanced and advanced adenoma, and CRC were 10.6%, 28% and 78.6%, respectively. However, there was a higher false-negative rate in detecting proximal advanced adenoma (sensitivity: proximal 24.1% vs distal neoplasm 34.3%, p=0.013), non-polypoid lesion (sensitivity: polypoid 31.1% vs non-polypoid neoplasm 21.1%, p<0.01) and early cancer (sensitivity: T1 cancer 66.7% vs T2–4 cancer 100%). The diagnostic performance of FIT was also unsatisfactory in a recent local study using FIT for the screening of CRC in patients with positive family history. The sensitivity of FIT in detecting adenoma, advanced neoplasm and cancer was only 9.5%, 35.1% and 25.0%, respectively.16 It is clear that a more sensitive test is needed.

Stool DNA testing has emerged as a sensitive test for CRC screening. In a recent study using a new multi-target stool DNA test which includes quantitative molecular assays for KRAS mutations, aberrant NDRG4 and BMP3 methylation, and β-actin, plus a haemoglobin immunoassay for screening of 459 asymptomatic subjects, at 90% specificity of the test, the sensitivity for diagnosing CRC was 98% (stage I, 95%; stage II, 100%; stage III, 96%; and stage IV, 100%). The sensitivities for advanced lesion (advanced adenoma and sessile serrated adenoma) ≥1 cm was 57%, >2 cm was 73%, and >3 cm was 83%.17

Another recent study used this multi-target stool DNA test in comparison with FIT. In 9,989 average-risk subjects screened, the sensitivities for detecting CRC, advanced lesions, polyps with high grade dysplasia and serrated polyps ≥1 cm were 92.3%, 42.4%, 69.2%, and 42.4% for DNA testing, as compared with 73.8%, 23.8%, 46.2% and 5.1% for FIT, respectively. In all comparisons, DNA testing was statistically significantly better than FIT. The numbers of people needed to be screened to detect one tumour were 154 with colonoscopy, 166 with DNA testing, and 208 with FIT. Further comparative studies with other screening methods and cost-effectiveness analysis are needed to clarify the role of stool DNA testing.

Endoscopy-based tests

Flexible sigmoidoscopy (FS) has been used for screening of distal colonic...
lesion; however, bowel preparation is still required. If any lesion is found in the distal colon, the patients should be referred for complete colonoscopy, up to 6.3% of patients may have synchronous proximal advanced lesions (compared with 1.5% when no lesion is found in the distal colon).19

From the UK Flexible Sigmoidoscopy Trial Investigators study, the effect of one-time FS screening of subjects aged 55–64 years was examined. This multi-centre, randomized controlled trial involved 170,432 subjects who were randomized to receive one-time FS or no screening. Screened subjects who had high-risk polyps were referred for colonoscopy (5% in the study), whereas subjects who had no polyps or only low-risk polyps were discharged. Median follow-up was 11.2 years and it was shown that CRC incidence was reduced by 23% in intention-to-treat and 33% in per-protocol analyses. Mortality was reduced by 43% in per-protocol analysis and incidence of distal CRC was reduced by 50%. The number needed to be screened to prevent one CRC diagnosis or death were 191 and 489, respectively. However, there was no significant protection of proximal CRC.20

In another US long-term follow-up study (PLCO cancer screening trial) involving 154,900 average-risk subjects randomized to FS or usual care, the CRC incidence was reduced by 21% and mortality reduced by 26% (50% reduction for distal colon cancer). The incidence of CRC in proximal colon was reduced by 14.4% to 20.7% for stage I–III cancer but only 2% in stage IV cancer. There was no reduction in the mortality rate.21

In recent randomized multi-centre studies in Spain (COLONOPREV study), using a colonoscopy screening database, the effect of FS (n=5,059) was artificially created and compared with biennial FIT screening (n=10,507). FS detected more advanced neoplasm (6.3% vs 2.7%, p<0.0001) and advanced distal neoplasm (odds ratio, 1.17; p=0.44) than FIT. It was seen that proximal lesion had a lower detection rate (FS: proximal 19.1%, distal 86.8% vs FIT: proximal 14.9%, distal 33.5%).22 Therefore, if complete colon examination is required, further structural examination is needed.

**Colonoscopy**

Colonoscopy can examine the whole colon and remove both polyps and pre-malignant lesions when encountered. However, the requirement of bowel preparation, sedation for the procedure, higher cost and complication rate means the examination is not suitable for all.

As discussed previously, the National Polyp Study confirmed the benefit of regular colonoscopy screening of average-risk subjects to reduce CRC.2 The Nurses’ Health Study and the Health Professionals Follow-up Studies demonstrated that in a long-term follow-up period (>22 years) of 88,902 participants, there were 1,815 new cases and 474 deaths from CRC. When comparing those without lower endoscopy examination with those who had a lower endoscopy (FS or colonoscopy), the incidence of distal CRC was reduced after polypectomy (multivariate hazard ratio (MHR) 0.40; 95% CI, 0.27 to 0.59), as well as after a negative FS (MHR, 0.44; 95% CI, 0.36 to 0.53) and after a negative colonoscopy (MHR, 0.24; 95% CI, 0.18 to 0.32). However, a negative colonoscopy was associated with a significantly reduced risk of proximal colon cancer (MHR, 0.73; 95% CI, 0.57 to 0.92). The estimated CRC prevented by colonoscopy was 40% for all CRC, 22% for proximal and 61% for distal CRC. In addition, reduced risks were observed up to 15 years after the last negative colonoscopy for both proximal colon cancer (MHR for 5.1 to 15.0 years, 0.60; 95% CI, 0.38 to 0.94) and distal CRC (MHR for 5.1 to 15.0 years, 0.35; 95% CI, 0.22 to 0.54). Only screening colonoscopy was associated with reduced mortality from both distal CRC (MHR, 0.18; 95% CI, 0.10 to 0.31) and proximal colon cancer (MHR, 0.47; 95% CI, 0.29 to 0.76), whereas screening sigmoidoscopy was only associated with reduced mortality from distal CRC (MHR, 0.31; 95% CI, 0.20 to 0.49).23

The question remains as to why in colonoscopy, that inspects the whole colon during an examination, the protection for the proximal colon is less than the distal colon? It may potentially be due to inadequate bowel preparation obscuring the proximal colon, or the presence of flat non-polypoid sessile serrated lesions in the proximal colon (around 6–10%).24 These lesions are more difficult to detect and may be associated with advanced pathology.25 It stresses the importance of a high quality colonoscopy examination to maximize the protection. An indicator that may reflect the quality is the colonoscopists’ adenoma detection rate (ADR). Data from the Poland national CRC screening programme noted the ADR to be closely related to the risk of interval CRC after screening colonoscopy.26 Increasing the scope withdrawal time,27 using image-enhanced endoscopy techniques such as narrow band imaging,28 or using auxiliary equipments may help to improve the ADR.29

**Capsule endoscopy**

Colon capsule endoscopy (CE) is a non-invasive technique to visualize the whole colon. A second-generation colon capsule endoscopy system (PillCam Colon 2) has been developed to increase sensitivity for colorectal polyp detection. In one study, the sensitivity and specificity for polyps ≥10 mm were 88% and 95%, and for polyps ≥6 mm were 84% and 64%, respectively.30 However, the bowel preparation requirement for colon CE is higher than conventional colonoscopy and if lesions are found during CE, a formal colonoscopy is still needed. The screening interval has not yet been determined.

**CT colonography**

CT colonography (CTC) is a less invasive alternative method for structural colon examination. American College of Radiology has recommended CTC for CRC.
screening and it should be repeated every 5 years after a negative result. A concern is that small and flat lesions may be missed by CTC as, according to the CT colonography reporting and data system (C-RADS) guidelines, any isolated diminutive polyps <6 mm (representing approximately 76% of all polyp diseases) were neither identified nor reported. For isolated 6–9 mm polyps, imaging surveillance was provided or the patient may be referred for colonoscopy. However, these small polyps may harbour high-grade lesions so there may be a chance of developing interval cancer between screening periods. The safety of CTC screening was recently tested, a 1,011 patient cohort was studied all with a negative CTC and an average of 4.7 years follow up. One incident CRC was detected during follow up, representing a crude cancer incidence of 0.2/1,000 patient years, compared with 1.7–2.4/1000 patient years, compared with 1.7–2.4/1000 patient years in colonoscopy surveillance cohorts from literature. Additionally 11 advanced adenomas, one appendiceal mucinous adenomas, one appendiceal goblet cell carcinoid were identified. It was concluded that clinically significant tumours are rare 5 years after a negative CTC and supports the current 5 year surveillance guideline.

In CTC examination, bowel preparation is still required and there is a risk of radiation exposure. CTC may lead to unnecessary investigations and treatment for other extracolonic abnormalities detected during the examination.

**Conclusion**

More new evidence appears to support CRC screening for an average-risk population. Any form of screening is better than no screening in preventing CRC incidence and reducing mortality; however, the choice of screening method will depend on patient preference and cost consideration. Physicians should encourage patients to participate in a screening programme.

**References**

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Update in the Management of Mantle Cell Lymphoma

Introduction

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Mantle cell lymphoma (MCL) arises from malignant transformation of B-lymphocytes in the outer edge of a lymph node follicle (the mantle zone). MCL is a rare B-cell NHL that most commonly affects men over the age of 60.

Clinical presentation

Most patients initially present with stage III–IV generalized, non-bulky lymphadenopathy, often with extranodal involvement. The bone marrow, tonsils, spleen, liver and gastrointestinal (GI) tract are among the most common extranodal sites. There is a tendency for MCL to invade the GI tract, which may present as a distinctive syndrome of multiple lymphomatous polyposis of the large bowel. Even patients without overt colonic polyposis are frequently seen to have subclinical GI epithelial invasion when investigated by biopsy.

Diagnosis

Diagnosis is based on lymph node, bone marrow, or tissue morphology of centrocytic lymphocytes, small cell type, or blastoid variant cells. The majority of MCL consists of small lymphocytes with notched nuclei. The aggressive variant is blastoid and pleomorphic.

Characteristic cell surface protein expression involves monoclonal B cells that co-express CD5, a normal T cell marker, but not CD23, differentiating MCL from the more common CD5+ B cell disorder chronic lymphocytic leukaemia (CLL).

A chromosomal translocation t(11;14) is the molecular hallmark of MCL, resulting in the overexpression of cyclin D1 which is detected by immunohistochemistry in 98% of cases. The absence of SOX-11 or a low Ki-67 may correlate with a more indolent form of MCL. The differential diagnosis of MCL includes small lymphocytic lymphoma, marginal zone lymphoma, and follicular lymphoma.

Risk stratification

The International Prognostic Index (IPI) was first developed for patients with diffuse large B-cell non-Hodgkin lymphoma. This was used for patients with MCL, but was not very discriminatory, particularly for lower-risk patients. More recently a prognostic index for MCL, the mantle cell international prognostic index (MIPI), was formulated by the European MCL Network. The independent prognostic factors for shorter overall survival in the MIPI were higher age, worse ECOG (Eastern Cooperative Oncology Group) performance status, higher LDH (lactate dehydrogenase), and a higher white blood cell count at diagnosis. These were calculated and three groups emerged: MIPI low-risk with the median overall survival (OS) not reached (5-year OS 60%), MIPI intermediate risk with a median OS of 51 months, and a MIPI high risk group with a median OS of 29 months (Figure 1).

Key words:
Mantle cell lymphoma (套細胞淋巴瘤), Bendamustine (苯达莫司汀), Ibrutinib (依鲁替尼)
A simplified version of the MIPI has also been developed which has high concordance to the original MIPI, but slightly less discriminatory power. The addition of the Ki-67 proliferation index also provides some additional discriminatory power (Table 2). For each prognostic factor, 0–3 points are given and the points are summed, up to a maximum of 11. Patients with 0–3 points are low risk, patients with 4–5 points are intermediate risk, and patients with 6–11 points are high risk. These risk categories correspond to the categories of the original MIPI.

### Risk-adapted therapy

Mantle cell lymphoma is responsive to a variety of initial therapies, but relatively short-term remission is achieved with conventional chemotherapy regimens. The median duration of remission in most trials is 1.5–3 years and the median OS is 3–6 years with standard chemotherapy. However, there is a wide variation in outcomes with some patients having a very aggressive presentation and succumbing to their disease in a short period of time, while other patients at the opposite end of the spectrum have a very indolent clinical course.

Given the unfavourable prognosis and the knowledge that standard therapy does not appear to cure patients with MCL, a “watch and wait” strategy for patients with asymptomatic, low MIPI or elderly MCL patients should be considered. Whereas, for younger patients with intermediate- or high-risk MIPI MCL, aggressive therapy with a cytarabine-containing regimen ± stem cell transplantation should be considered. For older MCL patients with intermediate- or high-risk MIPI, combination chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-bendamustine (BR) therapy, should be considered. A randomized trial carried out in Europe compared R-CHOP to R-bendamustine in a number of different lymphomas. In this trial, the patients with MCL had a similar ORR (89% for BR and 95% for R-CHOP). The BR regimen was associated with a lower progression rate of 42% vs. 63% for the R-CHOP arm. In addition, the haematologic toxicity and alopecia were less in the R-bendamustine arm.

After relapse, agents directed at activated pathways in MCL cells such as bortezomib (NFkB inhibitor) or lenalidomide (anti-angiogenesis) are approved. Ibrutinib (Bruton’s tyrosine kinase inhibitor) or idelalisib (phosphoinositide 3-kinase inhibitor) have also demonstrated excellent clinical activity in MCL patients. Autologous or allogeneic stem cell transplantation can be considered in young patients. Allogeneic stem cell transplantation still remains the only known curative therapeutic option in MCL but is not available to the majority of MCL patients, who are generally of older age.

### Novel agents

In June 2013, the FDA approved the oral thalidomide analogue lenalidomide for the treatment of MCL that had relapsed or progressed after two prior therapies including bortezomib, a subcutaneous therapy that has been available for MCL since 2006. Ibrutinib is the third drug approved to treat MCL, it works by blocking Bruton’s tyrosine kinase, a mediator of the B-cell receptor that has been shown to inhibit malignant B-cell survival. Ibrutinib’s approval is based on a phase II study of 111 patients with relapsed or refractory MCL after a median of three prior therapies. It reporting an overall response rate of 66% at a daily dose of 560 mg ibrutinib and the median duration of response was 17.5 months.

### Conclusion

Although median survival of MCL has typically been in the range of 3–4 years, recent trials have reported survival of 5–7 years. In addition to the introduction of dose-intensified regimens, the advent of effective rescue medication has probably made a major contribution.

### References

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