INTRODUCTION
Colorectal cancer is a major public health problem leading to cancer mortality in the world. The problem of cancer in Malaysia is growing one and consider as the fourth cause of death among medically certified death (5).

The incidence of colorectal cancer (CRC) varies approximately 20-fold around the world, with the high rates seen in industrialized countries such as North America, Australia and New Zealand, and the lowest in India (6). Although CRC exhibits universal distribution, there is a higher incidence of the disease in developed, industrialized countries, such as North America, Northern Europe and New Zealand. The disease is less common in South America, Southeast Asia, Equatorial Africa and India (7).

Colorectal cancer is currently one of the most common cancers in Malaysia. The second report of the National Cancer Registry mentions that colon cancer is ranked as the third most frequent cancer with rectal cancer being ranked as the 5th most common cancer among both males and females in peninsular Malaysia. The incidence of colon cancer in Chinese is two times higher compared to other ethnic groups. Colorectal cancer incidence among Malaysians increases after 50 years in both males and females (8). In Penang Cancer Registry report, the incidence rate for colon cancer was 115.9 per 100,000 for males and 119.7 per 100,000 for females (9). Data from the Ministry of Health of Malaysia declared an increase in colorectal cancer admission rates from 8.1% in 1987 to 11.9% in 1995. Genetics, experimental, and epidemiological data suggest that colorectal cancer develops from complex interactions between inherited susceptibility and environmental factors. The current hypothesis is that adenomatous polyps are the precursors of the vast majority of colorectal cancers. Thus measures that can detect and reduce the prevalence of these adenomatous polyps can reduce the risk of colorectal cancer (10). The etiology of CRC remains unclear. However, many factors such as hereditary, age, inflammatory bowel disease, environment as well as lifestyle have been found to be associated with CRC (11).

Approximately 5-10% of all CRCs develop in the setting of hereditary cancer syndromes, mainly familial adenomatous polyposis syndrome. A family history of CRC in a first-degree relative as parents, sibling, or offspring presents a high risk factor especially where the person developed cancer before the age of 45. However, the majority of CRCs (85%) are sporadic and not associated with a known inherited syndrome or genetic predisposition (12). Much experimental and epidemiological evidence suggest that the high fat diets, particularly animal fat and red meat increase the risk of CRC, whereas the consumption of vegetables, fruit and fiber reduces the risk of CRC (13).

Colorectal cancer screening is complex, as there are multiple options; it requires considerable patient effort (fecal occult blood test slides, colonoscopy preparation, etc.). For a screening program to be successful, multiple events have to occur, such as awareness and recommendation from the primary care physician, patient acceptance, financial coverage, risk stratification, screening test, timely diagnosis, timely treatment, and appropriate follow-up. If any one of these steps is faulty or is not of high quality, the screening will fail (14). The early screening and detection, removal of carcinomas and adenomas may prevent colorectal cancer deaths (15).

The double contrast barium enema (DCBE) is a radiologic test in which barium and air are instilled in the colon and x-rays are made in various positions. Patients were usually prepared for the test with a night laxative, a clear liquid diet and 1 or 2 morning enemas before the examination. The examination itself takes 20 to 40 minutes, no sedation is used. If the test is positive, a colonoscopy is performed; if it is negative, it is repeated in 5 years (16).
In many parts of the world, colonoscopy is used as a primary screening tool on a case-finding basis. It is, of course, highly accurate with a specificity of 100% and a very high sensitivity, although it should be emphasized that sensitivity is not 100%, as back-to-back colonoscopy studies have shown that adenomas and occasionally carcinomas can be overlooked even by experienced colonoscopists (17). No testing interval has been examined empirically, though testing every 10 years is the most commonly considered strategy. Some experts have advocated a once in a life time examination between 55 and 65years of age (18).

There are many biomarkers for colorectal cancer that can be measured in the body fluids of the patients with risk of cancer. These markers include carcinoembryonic antigen CA-195, CA-125 and CA-50 but lack of specificity makes these markers inappropriate to be used as screening tool (19).

Anticancer drugs comprise one of the three principle modalities of treatment offered to a patient with a malignancy, the other two being surgery and radiotherapy (20). Chemotherapy was developed in 1940s. Modern cytotoxic agents have become available for the treatment of colon cancer in recent years (19). The chemotherapy after colonic resection is indicated for patients with positive lymph nodes or Stage C disease (21). For almost 50 years, 5-fluorouracil (5-FU) has been the cornerstone of systemic cytotoxic chemotherapy for patients with metastatic CRC. In recent years, many important new treatment options have been developed, which changed the outcome for patients with metastatic CRC. Capecitabine (Xeloda) is an orally-administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers. It is a pre-produrg of 5-FU and is rapidly converted to 5-FU in tumor tissue. Thymidylate synthesis inhibition and incorporation into RNA and DNA are the most important mechanisms of action of capecitabine (22).

After oral administration, capecitabine is rapidly taken up from the gut and converted into first metabolized to 5'-DFCR, which takes place mainly in the liver by carboxylesterase. The metabolite is converted to 5'-DFUR by cytidine deaminase in liver and tumor tissue and converted to 5-FU intracellular by thymidine phosphorylase, an enzyme that is often expressed in tumor tissue. Combination with food intake significantly reduces the systemic exposure to capecitabine. It is recommended to take the drug after a meal because this has also been done in the clinical trials. The time to reach the maximal plasma concentration after food ingestion is around 2 hours. Oral pharmacokinetics are linear, the absolute bio-availability is estimated to be 40%-45% (23). Catalytic inactivation of 5-FU proceed by dihydropyrimidine dehydrogenase (DPD), which is polymorphically expressed. Capecitabine is largely eliminated as metabolites (> 95% of the dose). The terminal half-life of the parent drug and its metabolites is short (<1 hour). Excretion proceeds via the urine. No clinically relevant demographic factor or ethnic differences affecting the pharmacokinetics have been found to date (22). No relevant effect of age was found on the disposition of 5-FU after capecitabine therapy, although wide variability in the pharmacokinetics may have masked a true relationship between age and 5-FU pharmacokinetics (24).

The usual starting dose is 2,500 mg/m²/day in two divided doses, 12 hours apart. One cycle includes two weeks of treatment followed by one week without treatment. Cycles can be repeated every three weeks (25). Lower doses are used often when it is given in combination with irinotecan or oxaliplatin or in patients with renal insufficiency. The dose should be taken on a full stomach with breakfast and dinner. The convenience of oral administration and an improvement in toxicity makes capecitabine a useful alternative to intravenous 5-FU both by itself and incorporated into other regimens used in colon cancer (26). Side Effects of capecitabine include abdominal disturbance, generalized pain, weakness, blurred vision and haematological toxicity: Includes anaemia, leucopenia and thrombocytopenia (27).

METHODOLOGY

15 Patients (7 prospective and 8 retrospective) with histological diagnosis of carcinoma colon were included in the study. The age, gender, race, histological review and stage were recognize in this study. All cases of carcinoma colon histologically proven and planed for Capecitabine based chemotherapy and patients with good performance status ECOG 1-2 (Eastern cooperative oncology group) were chosen.

Patients with underlying psychiatric illness, ischemic heart disease, renal impairment and severe hepatic dysfunction were excluded from this study. The study was approved by the Ethics Committee of the Advanced Medical and dental Institute Universiti Sains Malaysia. All the patients accepted blood examination. The blood samples were retrieved from patients with carcinoma colon attending oncology department and planed for capecitabine based chemotherapy regimen at Kepala Batas Hospital. A Haematological toxicity of chemotherapy was assessed in 15 patients and single agent capecitabine in standard dose of 1,250 gm/m². For prospective patients, blood sample was collected before Capecitabine chemotherapy and after (2 weeks) when finish first cycle and for testing full blood count (FBC) by using automatic haematological analyzer (Sysmex KX-21) was used which includes (Erythrocyte count, Haemoglobin level, Haematocrit level, Mean Corpuscular Volume (MCV), Mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration(MCHC), leucocyte count, Platelet count, Differential and platelets count). For retrospective patients we observe the full blood count for all these parameters after complete one and 8 cycles of capecitabine chemotherapy.

We used the statistical package for social science (SPSS for windows, version 12; SPSS) for analysis of the data. The Paired Samples t-Test compares the means of two variables. All the data are presented as means ± standard deviation. Differences were considered significant statistically for two sided P values if ≤ 0.05.

RESULTS

All colon carcinomas were histologically proven as adenocarcinoma, they stage from II and above. The results of age, gender and race are summarized in Figures (1, 2, 3) respectively. The study showed that there was no significant haematological toxicity in using single agent capecitabine in standard dose of 1,250 gm/m² for first two weeks prospectively for all full blood count parameters except MCH (P value ≤ 0.05 (0.022)) in patients with colon cancer. However there was also no significant haematological toxicity in retrospective patients after completing one and 8 cycle’s capecitabine chemotherapy. All the result tabulated in Table 1 and Table 2.
DISCUSSION

The purpose of the study was to find whether capecitabine based chemotherapy is safe haematologically or not in patients with colon carcinoma in sample population, as data on usage of capecitabine is still evolving. The full blood count parameters were evaluated pre and post chemotherapy and tolerance in terms of haematological toxicity was assessed. The present study showed that capecitabine does not cause significant haematological toxicity. All major full blood count parameters remained within normal range. A Study by Myung-Ju showed significant activity and favorable toxicity in patients with colorectal cancer. The most common haematological toxicities were grades I/II anaemia (45%), leucopenia (33.75%) and thrombocytopenia (17.5%).The study found safety of capecitabine in combination with oxaliplatin (29). Fluoropyrimidine (5 Fluorouracil (5FU) and capecitabine) based regimens FOLFOX6 (5FU, Leucovorin, oxaliplatin) CapeOX (Capecitabine and Oxaliplatin) with or without Bevacuzumab and found out that these regimens are well tolerated. Only 6% of patient developed anaemia, 2% leucopenia and 15% thrombocytopena of grade 3 or 4 severity with CapeOX regimen (30). So far capecitabine has been combined safely with oxaliplatin and single agent as well, but data is limited in Asian population and especially in Malaysia.

In a study with metastatic colorectal cancer Patients (n = 1207), a safety profile of capecitabine using data from a large, well-characterized population of patients with metastatic colorectal cancer treated in two phase III studies was evaluated, patients were randomized to either oral capecitabine (1250 mg/m² twice daily, on days 1–14 every 21 days) or intravenous (i.v.) bolus 5-FU/leucovorin. Capecitabine demonstrated a safety profile superior to that of 5-FU/leucovorin, with a significantly lower incidence of diarrhea, stomatitis, nausea, alopecia and grade 3 or 4 neutropenia leading to significantly fewer neutropenic, fever/sepsis and fewer hospitalizations. All patients in the capecitabine group received a starting dose of 1250 mg/m² twice daily and the majority (66%) did not require dose modification for adverse events (31).

As in our study we compare the full blood count before and after first cycle of capecitabine prospectively and after first and 8 cycle retrospectively, there was no significant difference so it can suggest that the haematological toxicity may be not start after the first cycle, however we found that even retrospectively our 8 patients did not show any significant haematological toxicity even after they finish their 8 cycle. Even its not agreed by other studies but it may suggested that the drug is more tolerable in different Asian country if used as a single drugs or because of small sample size .In future studies we need bigger sample size including prospective study design to assess hematological toxicity.

CONCLUSION

Capecitabine is at least as effective, better tolerated and more convenient than i.v. drugs as treatment for patients with colorectal cancer. It is concluded that capecitabine based chemotherapy is haematologically tolerant from the first cycle until the end of cycles if used as a single drug in the treatment of colon carcinoma in Asian populations.

REFERENCES


### Table I: Haematological parameters for prospective patients before and after one cycle capecitabine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Value</th>
<th>Before chemotherapy Mean (SD)</th>
<th>After chemotherapy Mean (SD)</th>
<th>t-statistic (df)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>11.5-16.5 g/dL</td>
<td>12.11 (1.52)</td>
<td>12.087 (1.73)</td>
<td>0.14 (14)</td>
<td>0.890</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>37-47 %</td>
<td>36.08 (4.51)</td>
<td>35.627 (4.9)</td>
<td>0.712 (14)</td>
<td>0.488</td>
</tr>
<tr>
<td>RBC</td>
<td>3.8-5.8 x10^6</td>
<td>3.77 (0.55)</td>
<td>3.688 (0.52)</td>
<td>1.131 (14)</td>
<td>0.277</td>
</tr>
<tr>
<td>MCV</td>
<td>76-96 fl</td>
<td>90.2 (24.62)</td>
<td>97.193 (7.79)</td>
<td>-1.124 (14)</td>
<td>0.280</td>
</tr>
<tr>
<td>MCH</td>
<td>27-32 pg</td>
<td>32.29 (3.05)</td>
<td>32.97 (2.983)</td>
<td>-2.57 (14)</td>
<td>0.022*</td>
</tr>
<tr>
<td>MCHC</td>
<td>30-35 g/dl</td>
<td>33.55 (0.95)</td>
<td>33.84 (0.73)</td>
<td>-1.025 (14)</td>
<td>0.323</td>
</tr>
</tbody>
</table>

Paired t-test, df=Degree of Freedom, SD= Standard Deviation

### Table II: Haematological parameters for retrospective patients after one cycle and 8 cycle capecitabine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Value</th>
<th>After one cycle chemotherapy Mean (SD)</th>
<th>After 8 cycles chemotherapy Mean (SD)</th>
<th>Difference of Mean (95%CI)</th>
<th>t-statistic (df)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>11.5-16.5 g/dl</td>
<td>11.9 (0.91)</td>
<td>11.9 (0.89)</td>
<td>-0.05 (1.21,1.16)</td>
<td>-0.50 (7)</td>
<td>0.962</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>37-47 %</td>
<td>36.5 (1.50)</td>
<td>36.7 (1.40)</td>
<td>-0.25 (2.05,1.80)</td>
<td>-0.154 (7)</td>
<td>0.882</td>
</tr>
<tr>
<td>RBC</td>
<td>3.8-5.8 x10^6</td>
<td>4.12 (0.40)</td>
<td>4.2 (0.40)</td>
<td>-0.08 (-0.45,0.37)</td>
<td>-0.253 (7)</td>
<td>0.807</td>
</tr>
<tr>
<td>MCV</td>
<td>76-96 fl</td>
<td>89.2 (7.98)</td>
<td>88.5 (8.37)</td>
<td>1.38 (6.07,7.41)</td>
<td>0.042 (7)</td>
<td>.816</td>
</tr>
<tr>
<td>MCH</td>
<td>27-32 pg</td>
<td>29.1 (2.94)</td>
<td>28.9 (3.09)</td>
<td>0.4 (-2.2,2.6)</td>
<td>.184 (7)</td>
<td>.859</td>
</tr>
<tr>
<td>MCHC</td>
<td>30-35 g/dl</td>
<td>32.5 (1.27)</td>
<td>32.5 (1.32)</td>
<td>0.1 (-1.6,1.7)</td>
<td>.073 (7)</td>
<td>.944</td>
</tr>
<tr>
<td>WBC</td>
<td>4.1-1 x10^7</td>
<td>7.5 (2.81)</td>
<td>7.25 (2.14)</td>
<td>0.4 (-0.92,1.32)</td>
<td>0.425 (7)</td>
<td>.684</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>37-72 %</td>
<td>63.9 (8.85)</td>
<td>63.1 (7.85)</td>
<td>1.46 (-3.8,5.26)</td>
<td>0.093 (7)</td>
<td>.706</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>20-45 %</td>
<td>29.8 (5.85)</td>
<td>29.5 (4.81)</td>
<td>0.5 (-2.4,2.9)</td>
<td>.221 (7)</td>
<td>.831</td>
</tr>
<tr>
<td>Platelet</td>
<td>130-400 x 10^9</td>
<td>278.9 (64.26)</td>
<td>293.4 (57.52)</td>
<td>-29 (-55.8,26.8)</td>
<td>-0.831 (7)</td>
<td>.433</td>
</tr>
</tbody>
</table>

Paired t-test, df=Degree of Freedom, SD= Standard Deviation
Figure 1: Age distribution among sample population (years).

Figure 2: Gender distribution among sample population.

Figure 3: Race distribution among sample population.