The advanced colorectal cancer biology essay

Science, Biology

Colorectal cancer(CRC) is defined as the cancerous growth of epithelium lining in the colon and rectum1. Colon and rectum are part of the large intestine in the digestive system. CRC is usually developed from the adenomatous polyps which are usually benign, but it can develop into cancerous over time2, 3. Majority of the CRC are sporadic(~95%) while a low percentage is hereditary. Hereditary CRC are primarily caused by an inherited genetic defect for example the familial adenomatous polyposis(FAP) and the hereditary non-polyposis colon cancer(HNPCC) 3, 4, 5. Both sporadic and familial cases have similar pathophysiology. The two main pathophysiology of CRC are the genomic instability and epigenetic factors. The genomic instability consists of the chromosomal instability(CIN) and microsatellite instability(MSI) while the epigenetic factors are the genetic control by factors other than the DNA sequences, it is responsible to switch genes on or off to determine which proteins to transcribe3, 4, 5. The dysplastic aberrant crypt focus(ACF) is the precursor lesion that able to identify in the CIN-pathway3. The CIN pathway is associated with mutation in the adenomatous polyposis coli(APC) or loss of chromosome 5q where the APC genes located3, 5. One of the consequences of dysfunction APC is FAP3, 5. In CIN-pathway, the mutation of K-ras causes the activation of the RAS-RAF-MAPK signalling-pathway which promotes the cell proliferation5. The loss of heterozygosity(LOH) of 18q where the DCC, SMAD2 and SMAD4, the tumour suppressor genes are located will also leads to advanced adenoma3, 5. Lastly, the LOH of 17p and mutations p53 have deregulated the cell cycle, caused cells resistance to undergo apoptosis and finally transit the benign lesion into invasive disease5. The other chief mechanism of genomic

instability is MSI. It is known as the result of the mutation of the DNA mismatch repair (MMR) system which accountable for the repairs of DNA base-pair mismatches during the DNA replication3, 5. The inactivation of MMR is owing to the germ-line mutations of the hMLH1, hMLH13, hMSH2, hMSH3 and is the cause of the colon cancer family syndrome, the HNPCC3, 5. The inactivated MMR system also account for the sporadic CRC due to the aberrant methylation of hMLH13, 5. DNA methylation is the epigenetic factor of CRC. It occurs at 70% of the CpG dinucleotide. The high concentration of CpG region are free of methylation in normal cells2, 3, 4, 5. In cancer, the CpG islands become extensively methylated and caused the genes to turn off the tumour suppressor genes which eventually leads to CRC2, 3. 4, 5. Other than that, the risk factors such as gender, age, inflammatory bowel disease, diet, alcohol, and smoking will also increase the probability to develop CRC2. There are few stages of CRC, being categorized from stage A to D according to the Dukes classification. Stage A is where the cancer cell lying on the innermost lining of the colon or rectum with slight penetration into the submocosa, stage B1 extends beyond the submucosa into the muscularis propria whereas B2 into the serosa, stage C is where the cancer cells have spread to the lymph nodes near the colon or rectum and stage D is where distant metastasis takes place6. The most common sites of metastasis are the regional lymph nodes and the liver6. The tumour-node-metastases (TNM) classification has divide CRC into four stages. Stage 1 is corresponds to Stage A or B1, stage 2 corresponds to B2, stage 3 corresponds to stage C and lastly stage 4 corresponds to stage D6. The case scenario describes the patient is with advanced CRC. The advanced stage of

CRC is when the cancer has spread locally or to other parts of the body from the bowel or rectum which relates to stage 3 and 47. CRC has great impact on the society especially the elderly. The study done by the A. H. Fatima et al shown that the incidence rate of CRC is 50 times higher in people aged 60 to 79 than people younger than 408. According to the Cancer Research UK, CRC is the second most common cause of cancer death in the UK where there were 16, 013 people died due to CRC year of 20109. Generally, CRC tends not to produce signs and symptoms until it is advanced. The symptoms of CRC are highly depending on the site and size of the cancer as well as the presence of metastasis. Patients with CRC usually will experience abdominal pain, altered bowel habits which caused by diarrhoea and constipation, in addition of rectal bleeding. The less common one will be nausea, vomiting, and malaise. Advanced CRC patients will experience pain and particularly with metastasis will normally suffer from cachexia which includes involuntary weight loss, anorexia, fatigue, and muscle weakness7. CRC will cause patient suffer from iron deficiency anaemia due to the severe bleeding from rectal and produce koilonychias, the abnormally thin nails, weakness, dyspnoea or palpitation. Glossitis and cheilitis are also commonly found in CRC patient7. Besides that, patient with CRC also tends to develop cardiovascular disease, hypertension and hepatomegaly due to the hepatic metastasis7, 10. The prevalence of co-morbidity increases by age10. The survival rate of CRC depends on the stage at diagnosis. The overall 5-year survival rate was 50% but it was significantly different between the stages during diagnosis. In the study conducted by Aravani A et al, there were about 93% of patients being diagnosed at the earliest stage of CRC and survived

five years from diagnosis. However, there were only 6% of those in advanced disease7. Unfortunately, most patients diagnosed with CRC already in advanced stage at presentation and thus their survival rate is greatly reduced11. Moreover, the study analysed how the sex difference affected the survival rate. Female patient has slightly higher 5-year survival rates compared to male patients. This study also showed that patient who are younger than 60years old with CRC have noticeably higher 5-year survival rate compared to those older than 607. Other than that, the societal cost of CRC is also substantial. There was loss of £10 billion productivity costs estimated by Centres for Disease Control and Prevention based on persons who died from CRC12.

2. 0 Treatment Options for Elderly Patient with Advanced Colorectal Cancer

The case scenario given is a 72 year old male with advanced CRC. The standard treatment options for CRC are the chemotherapy and surgery 1, 13. 2. 1 Pharmacological TreatmentMonotherapyCapecitabineCapecitabine is a pro-drug that enzymatically generate 5-fluorouracil(5-FU) preferably at the tumour site14. 5-FU will inhibits DNA synthesis and cell division hence slows down the growth of tumour tissues15. The standard regimen of capecitabine is 1250mg/m2 twice daily for 14days and subsequent courses repeated after a 7-day interval15, 16. Many studies have proved that capecitabine is clinically effective to treat advanced CRC based on the result of its clinical trials. A large, randomised, controlled phase III trials has shown capecitabine is more effective with superior response rates(RR) compared to fluorouracil-leucovorin(FU/LV)17. Another study was conducted on 51 patients with

advanced CRC and age ≥70, it was observed that the overall RR was 24% including 4% of the patient with complete response, 20% with partial response, 43% with maintained stable disease and 33% had disease progression. The overall disease control achieved 67% which showed that capecitabine is effective on treating advanced CRC14. Plenty studies have shown that most cancer patients will prefer an oral route chemotherapy to an intravenous(IV) route as long as the efficacy remained16. Hence, the advantage of capecitabine being oral route has provides a patient-orientated chemotherapy also reduce the cost of IV administration in the hospitals. Besides that, several studies found that capecitabine has lower rate of grade 3-4 diarrhoea, stomatitis, nausea, and neutropenia14, 17. Capecitabine also found to be interacted with coumarins and caused over-anticoagulation especially in patient aged 60 years18, 19, 20. Therefore, if patients taking capecitabine with coumarins, prothrombin times should be monitored regularly and reduce dose of coumarins if necessary20. 2. 1. 1. 2OxaliplatinOxaliplatin is a di-amino-cyclohexane platinum complex which inhibits the synthesis of DNA selectively. It binds favourably to guanine and cytosine leads to the cross-linking of DNA and hence inhibits DNA synthesis21. Oxaliplatin achieved a 10% RR in three phase II trials involving 139 of metastatic CRC patients who were previously treated with 5-FU and achieved 20-24% of RR in recent two phase II trials on previously untreated metastatic CRC patients21. Many studies have proved that oxaliplatin is effective and with tolerated site effects on patient aged > 70years18. However, oxaliplatin will cause clinical toxicity. It is distinct from other platinum drugs with no renal toxicity and only caused mild hematotoxicity21,

22. It will also cause cold-related dysesthesia and a dose-limiting cumulative peripheral sensory neuropathy but both are reversible and can be rapidly eliminate after the treatment withdrawal21, 22. IrinotecanIrinotecan is a derivative of camptothecin that acts as an antineoplastic enzyme inhibitor which inhibits the action of topoisomerase I 23, 24. Irinotecan prevents re-ligation of the DNA strand by its binding on the topoisomerase I-DNA complex causes the double-stranded DNA break and apoptosis occur23. There are no fixed dose for irinotecan, the dose might be different in monotherapy and in combination, adjusted according to the patient's neutrophil count, renal and hepatic function and any previous adverse effects of cytotoxic drug23. According to Rougier et al, irinotecan has produced a higher RR compared to 5-FU but it also produced a higher grade3-4 toxicities such as vomiting, diarrhoea and neutropenia25. However, several studies have concluded that irinotecan is safe and effective for elderly patients and reduction of dose should not recommend24, 25, 26. A study conducted in UK has analysed the activity and toxicity of irinotecan according to age. The result obtained shows that there were no differences among the patients developing irinotecan-specific toxicity, response as well as OS according to age24. However, it is still important to undergo individual assessment for each elderly patients especially those > 80 years to initiate the suitable dose. Because of the dosage complexity and its higher probability to produce toxicity, it is not commonly prescribed as first-line monotherapy24, 25. Combination Therapy5-flurouracil with leucovorin with or without oxaliplatin5-FU was given as a single–agent to treat advanced CRC. However, it reached only 10% of objective responses in most

patients22. The RR now can be increased by combining 5-FU with LV. Plenty studies on combination of bolus 5-FU/LV and continuous 5-FU shown increase RR21, 22. The fluorouracil-based chemotherapy is the mainstay treatment of advanced CRC21. In recent years there have been consistent evidence in phase II trials showing that the clinical activity of combination 5-FU with LV and oxaliplatin(FOLFOX) has RR of 20% to > 50%21. There are different FOLFOX schedule depends on the way of 5-FU administer. Four phase IV trials on FOLFOX4 regimen were conducted and showed that patients with aged ≥70years achieved benefits in terms of RR, PFS and OS which is similar to younger patients18. Moreover, the de Gramont et al study also shown that FOLFOX patients have demonstrated a higher RR of 49. 5% compared to the 5-FU/LV patients group with only 28. 6%22. The dose intensity is the same between elderly and younger patients, thus suggesting that advancing age will not affect the drug delivery although elder patients tend to complete fewer treatment cycles18. Besides that, a study done in Japan by T. Shiroiwa et al has showed that FOLFOX is more cost-effective for stage 3 colon cancer compared to FU/LV therapy27. But this combination therapy has disadvantages. In the de Gramont et al study, they found that 41. 7% of FOLFOX patients have suffered from neutropenia, 5. 8% from grade3-4 vomiting and mucositis and 11. 9% from diarrhoea22. Patients might feel reluctant to take them if the side effects are severe and affect their daily life. Moreover, this combination therapy regimen needs continuous infusions which require venous access and carry infusion apparatus or fluids around. This will increase the inconvenience among patients as well as increase the risk of catheter-related complications for example infections and

thromboembolism27. Nevertheless, the elderly patients have achieved a relatively similar effect from this combination therapy compared to the younger patients22. The overall efficacy/safety ratio is also retained in elderly with CRC therefore we conclude that this combination is safe to administer to patients > 65year and particularly using as adjuvant and first-line settings18, 22. 2. 1. 2. 2 Irinotecan with 5-fluorouracil and leucovorinThe administration of the combination regimen of irinotecan with 5-FU/LV(FOLFIRI) has become more favourable due to the less toxic profile and a higher response rate presented in several stuies18. A number of phase II and III trials conducted have shown that the FOLFIRI is effective on advanced CRC patients28. A study done by L. B. Saltz et al involving patients previously untreated metastatic CRC aged 70-84years have shown an overall RR of 36. 6% and a median survival duration of 14. 5months18. The toxicities appeared in the study was generally controllable in both groups of patients. The outcomes of this study demonstrated a compatible efficacy and safety of FOLFIRI in elderly and younger patients18. The FOLFIRI and FOLFOX were compared by the experience of the Gruppo-Oncologico-dell'Italia-Meridionale(GOIM). Both proved to be effective and safe to treat advanced CRC patients and presented with different toxicity profile. FOLFIRI has caused more gastrointestinal side effects and alopecia while FOLFOX has caused more thrombocytopenia, neurotoxicity and hypersensitivity reactions28. Therefore, the choice of treatment in clinical practice should be individually tailored depends on the patients' response. 2. 1. 2. 3 Capecitabine with oxaliplatinGiven that the combination use of the capecitabine plus oxaliplatin would be interesting especially in elderly with

respect to the efficacy, safety and ease of administration. Various phase II and III studies have obtained similar efficacy and safety for combination of oxaliplatin with either capecitabine or 5-FU/LV27. Many studies investigated a type of combination of capecitabine and oxaliplatin, XELOX in elderly patients have shown good RR with 36-58% with a median OS of 13. 2-14. 4months18. A phase II clinical trial designed by J Feliu et al had recruited 50patients aged≥70years with metastatic CRC to receive XELOX. The result showed that the overall RR was 36%, 36% of patients had stable disease and 28% progressed. In this study, it was shown to have a median disease progression time at 5. 8months and OS time at 13. 2months27. This study has obtained a similar reading of RR and time to progression comparing with studies conducted by other authors with younger patients27. With this evidences, we can conclude that administering XELOX to elderly patients are as effective as to younger patients. Besides the effectiveness of XELOX, the ease of administration also should be put into consideration. The oral administration of capecitabine helps patients to avoid any potential complications and inconveniences associated with the use of infusion. Most elderly patients might need help from family members or carer to visit the hospital, the number of visit to hospital can be greatly reduced by implementing XELOX27. Nevertheless, a number of studies revealed XELOX caused adverse events like other cytotoxic drugs. The common adverse events of XELOX are diarrhoea, nausea, vomiting, hand-foot syndrome, neutropenia, and thrombocytopenia27. These adverse effects are quite similar to those found out on FOLFOX27. Targeted TherapyThere are three main types of targeted therapies, cetuximab, bevazixumab and

panitumumab but only cetuximab will be discuss here. CetuximabCetuximab is a chimeric Immunoglobulin G1(Ig G1)monoclonal antibody. It binds to the epidermal growth factor receptor(EGFR)which often over-expressed in CRC. Cetuximab competitively inhibit the binding of EGF factors to modulate tumour cell growth29. Cetuximab is able to function in monotherapy as well as combination therapy18, 29, 30. A phase II clinical trial of cetuximab monotherapy was tested on 57patients with EGFR-positive CRC who were refractory to 5-FU and irinotecan. It obtained 8. 8% of partial response and 36. 8% of them had stable disease30. As reported by D. Cunningham et al, the overall RR shown in combination therapy group(cetuximab with irinotecan) was 22. 9% whereas in monotherapy group was 10. 8%29. Another small trial was done by comparing monotherapy cetuximab with irinotecan with 5-FU/LV or in combination with irinotecan in patient aged ≥70 years. The result showed that combination therapy of cetuximab with iritonecan is safe and effective for elderly patients on refractory disease18. These studies demonstrated that cetuximab is able to treat iritonecan-refractory CRC by circumvent the iritonecan resistance29, 30. The incidence rate of hematotoxicity and other toxic effects in combination therapy of cituximab and iritonecan were similar to those reported in randomised studies of iritonecan30. However, most cetuximab clinical trials have reported acne-like or maculopapular rash. This is a side effect due to the blockade of EGFR because EGFR is responsible in maintaining the integrity of the skin18, 30. However, this side effect may be manage by individualised the dose according to the patients' response on the occurrence and severity of the rash30. 2. 2 Non-pharmacological TreatmentSurgery is the best

treatment for most CRC patients in stage 1 or 2 but it is not the case in advanced CRC13, 18. However, surgery can be considered for the case of obstruction or resectable hepatic metastases18. Some saying that the postoperative morbidity and mortality increased gradually with advancing age, but a study conducted in Japan comparing the impact of CRC liver metastases in patients ≥70 years and <70 years. They found that elderly patients are more likely to suffer from cardiopulmonary disease and respiratory deficiency but had similar post-operative complications compared to younger patients18. Even though elderly patients had lower the 5-year survival rate compared to the younger patients but at least surgery showed some disease improvement in advanced CRC. Therefore the decision to operate should not base on the age alone. In support of this, the stage of CRC at presentation, location of tumour and pre-existing comorbidities should also be put into consideration before patient undergoes surgery13. Hence, if elderly patient is healthy, receive preoperative assessment and good postoperative care, the patient should be considered for resection, surgical excision or palliative intraluminal procedures1, 13.

3. 0 Treatment Recommendation

The patient in the case scenario was said to be a 72 year old male patient with advanced CRC. There is lack of information in the case scenario to confirm the stage of CRC of the patient. As mentioned earlier, advanced CRC can be related to stage 3 or 4. Therefore, the patient should be offered a contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis to estimate the stage of the CRC31. This is because different

stage needs different type of treatment initiation. If patient is in stage 3, he should undergo surgery followed by adjuvant chemotherapy while if he is in stage 4, he should commence on chemotherapy with surgical intervention where appropriate1, 13, 31. There are three main treatment options, the monotherapy, combination therapy and target therapy. Out of the three main treatment options, combination therapy is often use nowadays due to the synergic effects performed on advanced CRC. The most effective combination chemotherapy treatments used to treat advanced CRC are the FOLFIRI and FOLFOX18, 28. There are plenty of evidence proposes that FOLFIRI and FOLFOX both are effective acting as a first-line treatment in treating advanced CRC showing different toxicity pattern that may affect the patient preference18, 28, 32. In a trial stated earlier, it stated that thrombocytopenia and neutropenia were more likely to be seen in patient receiving FOLFOX and fatigue and gastrointestinal side effects are more common in FOLFIRI18, 28. Another study also showed FOLFOX and FOLFIRI both have efficacy on treating advanced CRC but patient on FOLFOX have more common with grade3-4 toxicities compared to FOLFIRI (74% vs 53%), yet FOLFIRI has more frequent serious adverse events with 14% of the patient while FOLFOX only with 5% of the patients32. In the study conducted by Colucci G. et al, the RR obtained has no significantly difference between FOLFIRI and FOLFOX. However, the overall RR showed is more prone to FOLFOX than FOLFIRI (34% versus 31%). FOLFOX also has showed a higher rate on the 1-year survival rate at 62% whereas FOLFIRI only has 55%33. Hence, I will recommend the patient on FOLFOX regimen due to the higher response rate with the consideration of the patient’s condition, preference,

fitness, co-morbidity, response and the overall aim of the treatment18, 30. If the patient fails in his first-line treatment on FOLFOX, then the use of FOLFIRI regimen or iritonecan as a single-agent is the best choice as second-line treatment31, 34. A study to examine the use of FOLFIRI as second-line treatment in elderly advanced CRC patients following the failure of FOLFOX4 was conducted34. It showed that FOLFIRI has showed to improve patients overall survival even though most of the patients experienced severe grade3-4 adverse events especially neutropenia. The study suggested that this could probably because the toxicity of the previous treatment on FOLFOX has decreased the tolerability of second-line FOLFIRI on elderly patients34. Hence, if patient has suffered severe neutropenia in the first-line treatment, iritonecan may be a better choice for as a second-line treatment. There are several evidences proving that iritonecan is efficacious and safe to be used as a single-agent as second-line treatment in elderly advanced CRC patients24, 25, 26, 34. Furthermore, combination of cetuximab-FOLFIRI can be recommended to patients with EGFR-expressing, K-ras wild-type metastatic colorectal cancer1, 35. This combination therapy has showed reduced risk of progression by 15% as compared to the FOLFIRI treatment alone in metastasis CRC patients35. Yet, cetuximab can only prescribe to patients who have not previously received chemotherapy for their metastatic CRC and with liver metastasis that considered non-resectable1. Hence, cetuximab-FOLFIRI treatment can suggest to this patient if he is with EGFR CRC, but we should also consider the risk and benefit of this treatment since it has not much evidence of its safe and effectiveness in elderly CRC patients18. Last but not least, NICE-CG113 has suggested that the choice of

different combination of therapy should initiate only after the full discussion of the side effects with the patients30. Hence, the patient’s condition, preference, co-morbidity, as well as overall aim of the treatment has to put into consideration before prescribing any of the combination therapy.