*Early-stage colon cancer – EML*

The application sought endorsement of calcium folinate and fluorouracil (5-FU), already listed on the Model List of Essential Medicines, for the treatment of early-stage colon cancer. The application also sought the addition of oxaliplatin and capecitabine to the core list of the Model List for the same indication.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

**Introduction**

Surgical resection, the cornerstone of treatment in early disease, is potentially curative as a single-modality therapy in stage I, II and III colorectal cancer. Multiple clinical trials have demonstrated that 5-FU-based adjuvant chemotherapy can increase the cure rate of stage III colon cancer, and this is an option in countries with sufficient resources to administer chemotherapy and monitor its side-effects. In wealthy countries, the standard of care is the FOLFOX regimen (5-FU, calcium folinate, and oxaliplatin) or the CapeOx (XELOX) scheme (capecitabine and oxaliplatin), or single-agent capecitabine. In countries that cannot afford oxaliplatin, 5-FU/calcium folinate chemotherapy, administered as a weekly bolus, is still an effective regimen.

**Public health relevance**

Colorectal cancer is one of the most common, and deadly, malignancies; it has been estimated that there are 1.2 million new cases a year worldwide. Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and the third in women, killing an estimated 320 600 men and 288 100 women annually *(1)*.

In the developed world, the death rate from colorectal cancer has been falling, largely as a result of colonoscopy screening, which allows both the removal of precancerous polyps and the detection of early-stage, curable disease. Because 90% of colon cancers occur in patients who are at least 50 years old, the recommendation in countries that are able to afford colonoscopy is for screening of the general population to begin at age 50 *(2)*.

Because of the expense of colonoscopy, population-based screening programmes are not usually feasible in many parts of the world. Added to poor access to health care, this means that patients in low- and middle-income countries often present with more advanced stages of colorectal cancer.

In the United States, 40% of colorectal cancer patients have localized disease (stage I and II), 36% are regionally advanced (stage III) and 20% have metastases at presentation *(3)*.

**Requirements for diagnosis, testing, and administration**

*Diagnostics*

Localized colorectal cancer often presents with one of the following symptoms: change in bowel habits, blood in the stools, abdominal discomfort and weight loss. The symptoms of metastatic colorectal cancer depend on the site of metastasis (liver: right upper quadrant abdominal pain, jaundice; lungs: chest pain, shortness of breath).

The primary mass in colorectal cancer can be diagnosed by rectal examination, sigmoidoscopy or colonoscopy. A biopsy can be performed during endoscopy so that the diagnosis of cancer may be confirmed pathologically.

A critical aspect of the evaluation of a colorectal cancer patient is establishing whether metastatic disease is present. In high-resource health systems, computerized tomography scan of the chest, abdomen and pelvis is performed routinely. In resource-constrained settings, systemic evaluation with the less costly abdominal and pelvic ultrasound is commonly employed. Preoperative cancer staging, which evaluates the T and N stage of the tumour, is also important in establishing the degree of loco-regional invasiveness of the tumour. Where available, it is performed by either magnetic resonance imaging or endoscopic ultrasound, complex and highly specialized methods with limited availability in resource-constrained settings.

*Administration and care of patients*

Administration requires intravenous infusion capacity and regular patient access to clinical care. Treatment can be carried out in outpatient facilities; in settings where ambulatory infusion of 5-FU is not feasible it is common for patients to be treated in inpatient facilities. Antiemetics need to be available. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself. Importantly, inpatient facilities capable of supporting patients with severe infections and dehydration need to be readily available. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

There are several regimens of 5-FU/calcium folinate with equal efficacy. The modified de Gramont regimen is typically used because of its safety profile, but it requires continuous intravenous infusion of 5-FU over 46 hours and hence is more complex to administer. The Roswell Park regimen and single-agent oral capecitabine are alternatives that do not require infusional 5-FU. The corresponding oxaliplatin-containing regimes are FOLFOX, FLOX and CapeOx.

*Management of chemotherapy side-effects*

When chemotherapy is employed, laboratory evaluations play an important role in monitoring patient safety. A complete blood count with differential assesses whether patients are myelosuppressed and neutropenic. A comprehensive metabolic panel monitors renal and hepatic function as well as electrolyte imbalances.

**Overview of regimens**

*Surgery for stage I and II colon cancer*

For stage I and II disease, surgery alone is potentially curative and postoperative chemotherapy does not improve outcome. While there is considerable controversy, 5-FU-based chemotherapy may be beneficial in a highly selected patient population with stage II colon cancer (i.e. T4 tumours; poorly differentiated histology; lymphovascular or perineural invasion; perforated or obstructed lesion; fewer than 12 lymph nodes in the surgical specimen).

*Surgery and adjuvant chemotherapy for stage III colon cancer*

Surgery alone is potentially curative for stage III disease and should be used even in the absence of postoperative chemotherapy. The addition of postoperative chemotherapy to surgery increases the likelihood of a patient remaining disease-free and of improving overall survival.

*Standard regimens for stage III colon cancer*

- **Modified FOLFOX6 regimen (2-week cycle; 12 cycles)**
  - calcium folinate 400 mg/m$^2$ IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m$^2$ IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m$^2$ daily as continuous infusion over 46 hours (days 1 and 2 of each 14-day cycle)
  - oxaliplatin 85 mg/m$^2$ IV on day 1 of each 14-day cycle.

- **CapeOx (3-week cycle; 8 cycles)**
  - capecitabine 1000 mg/m$^2$ orally twice daily on days 1–14 of each 21-day cycle
  - oxaliplatin 130 mg/m$^2$ IV over 2 hours on day 1 of each 21-day cycle.

- **FLOX (8-week cycle; 3 cycles)**
  - 5-FU 500 mg/m$^2$ IV bolus weekly for 8-week cycle
  - calcium folinate 500 mg/m$^2$ IV weekly for 6 weeks of each 8-week cycle
  - oxaliplatin 85 mg/m$^2$ IV on day 1 of weeks 1, 3 and 5 of each 8-week cycle.

*Note:* It is acceptable to use low-dose calcium folinate, i.e. 20 mg/m$^2$ instead of higher doses *(4)*. Fixed-dose 50 mg calcium folinate is also an option.

*Acceptable regimens where oxaliplatin is unavailable or contraindicated*

- **Roswell Park regimen of adjuvant chemotherapy with 6 cycles of 5-FU and calcium folinate (6 months)**
  - calcium folinate 500 mg/m$^2$ IV bolus on days 1, 8, and 15 of each 28-day cycle (i.e. weeks 1, 2 and 3 of each 4-week cycle)
  - 5-FU 500 mg/m$^2$ IV bolus on days 1, 8 and 15 of each 28-day cycle (i.e. weeks 1, 2 and 3 of each 4-week cycle).

- **Modified de Gramont regimen of adjuvant chemotherapy with 12 cycles of 5-FU and calcium folinate (6 months)**
  - calcium folinate 400 mg/m$^2$ IV on day 1 of each 14-day cycle
  - 5-FU 400 mg/m$^2$ IV bolus on day 1 of each 14-day cycle
  - 5-FU 1200 mg/m$^2$ daily as continuous infusion over 46 hours (days 1 and 2 of each 14-day cycle).

- **Capecitabine as a single agent**
  - capecitabine 1000 – 1250 mg/m$^2$ twice daily for 14 days of each 21-day cycle for 8 cycles

*Note:* It is acceptable to use low-dose calcium folinate, i.e. 20 mg/m$^2$, instead of higher doses *(4)*. Fixed-dose 50 mg calcium folinate is also an option.

The Committee did not support use of the Mayo clinic regimen of bolus 5-FU, given that it is associated with greater toxicity than infusional 5-FU regimens: grade 3 or 4 neutropenia occurs more frequently (7.3% Mayo regimen versus 1.9% infusional regimen). Non-haematological toxicities such as diarrhoea (7.3% versus 1.9%) and mucositis (12.7% versus 1.9%) also occur more frequently *(5)*.

**Review of benefits and harms**

*Benefits*

Early-stage colon cancer is a potentially curable illness. The most critical treatment for patients with early-stage colon cancer is surgery: patients with stage I, II and III colon cancer can be cured with surgery alone. The survival rates for stage I and stage II are so high (the cancer-specific 5-year survival for stage I is greater than 95% and for stage II is 71–87%) that, even in developed countries, the vast majority of these patients are treated with surgery alone. The benefits – and therefore administration – of adjuvant chemotherapy in patients with stage II colon cancer remain unclear, although there is a subset of patients with high-risk clinicopathological features for whom adjuvant chemotherapy is, at a minimum, discussed.

Colon cancers that spread to regional lymph nodes, i.e. stage III cancers, have a higher risk of recurrence. Many clinical trials have demonstrated that adjuvant

chemotherapy lowers the risk of recurrence. Initial adjuvant therapy trials showed that adjuvant 5-FU, combined with either levisamole (an agent no longer used) or calcium folinate, reduced the risk of recurrence by 40% and the risk of death by 35% when compared with no adjuvant treatment *(6, 7)*. In one seminal inter-group trial, Moertel et al. demonstrated that for colorectal cancer patients with Dukes class C cancer (i.e. node-positive stage III disease) survival at 3.5 years was 55% for the observation arm and 71% for the 5-FU/levisamole arm *(7)*. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-03 study, an increase in both 3-year disease-free survival (73%; 95% CI: 69–77%, compared with 64%; 95% CI: 60–68%) and overall survival (84% vs 77%; $P = 0.007$) was recorded with bolus 5-FU and calcium folinate compared with lomustine, vincristine and 5-FU *(8)*. Similar benefit was noted in a study by the North Central Cancer Treatment Group, in which patients were randomly allocated to either bolus 5-FU and calcium folinate or observation, and in the International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) study, in which data were pooled from three separate trials undertaken in Canada, France and Italy. In the three IMPACT trials, patients received treatment based on one of two regimens: Roswell Park (RPMI), consisting of 500 mg/m² 5-FU and 500 mg/m² calcium folinate a week for 6 of 8 weeks; or Mayo, comprising 370–425 mg/m² 5-FU and 20 or 200 mg/m² calcium folinate daily for 5 days every 28 days. In subsequent trials, comparable clinical benefit has been noted between RPMI and Mayo bolus 5-FU regimens and between high-dose and low-dose calcium folinate. However, toxic effects differ between the RPMI and Mayo regimens: Mayo is associated with increased neutropenia and stomatitis, whereas RPMI leads to more cases of diarrhoea. Based on these differences, the RPMI regimen is generally preferred. One additional advantage of the RPMI regimen is that subsequent weekly doses can be delayed in the event of dose-limiting toxicity.

In addition to bolus regimens, those that include 5-FU infusions and oral capecitabine have been assessed. Several randomized studies show that, while infusional 5-FU regimens are not superior to the Mayo 5-FU and calcium folinate regimen, they are less toxic. In a phase III trial, capecitabine was non-inferior to the Mayo regimen in terms of disease-free survival and had fewer toxic effects. Three-year disease-free survival (64% vs 61%; $P = 0.05$) and overall survival (81% vs 78%; $P = 0.07$) were increased with capecitabine, although the difference was not statistically significantly. These results have been corroborated by a recent meta-analysis, which confirmed the non-inferiority of capecitabine *(9)*. In general, bolus and infusional 5-FU and oral capecitabine are acceptable options, and choice depends on local practices and economic considerations *(10)*.

The standard of care for adjuvant treatment of stage III colon cancer is now a combination of oxaliplatin and a fluoropyrimidine, such as FOLFOX and FLOX, which contain 5-FU, calcium folinate and oxaliplatin, or CapeOx, in which capecitabine, an oral drug, substitutes for 5-FU. The MOSAIC trial compared adjuvant FOLFOX4 with adjuvant 5-FU/calcium folinate. It demonstrated that FOLFOX4 improved survival in stage III colon cancer by 20% compared with 5-FU/calcium folinate *(11)*. The 6-year survival rate for stage III colon cancer patients treated with FOLFOX was 72.9% compared with 68.7% in patients

treated with 5-FU/calcium folinate *(11)*. The rate of grade 3 and 4 neutropenia was higher in the FOLFOX4 arm than in the 5-FU/calcium folinate arm (41.1% vs 4.7%) *(12)*. The rate of febrile neutropenia was also higher in the FOLFOX4 arm (1.8% vs 0.2%). Grade 3 neuropathy occurred in 12.4% of the patients treated with FOLFOX4 *(12)*. For ease of administration, most institutions use the modified FOLFOX6 regimen, in which the bolus of 5-FU on the second day of chemotherapy is eliminated.

The FLOX regimen was compared with 5-FU alone in the NSABP C-07 trial. For the intent-to-treat analysis, with both stage II and III patients included, the hazard ratio (HR) favouring FLOX was 0.82 and disease-free survival estimates at 5 years were 64.2% for 5-FU/calcium folinate and 69.4% for FLOX. For stage III patients, HR for disease-free survival was 0.78. Improvements in overall survival with FLOX compared with 5-FU/calcium folinate bordered on significance for stage III patients (HR 0.85; 95% CI: 0.72–1.00; $P = 0.052$). For stage III patients, the 5-year overall survival estimates were 73.8% for 5-FU/calcium folinate and 76.5% for FLOX *(13)*.

Similar results were obtained with the CapeOx (capecitabine and oxaliplatin) regimen, which improved progression-free survival compared with 5-FU/calcium folinate *(14)*. The 3-year disease-free survival rate was 70.9% with CapeOx and 66.5% with 5-FU/calcium folinate. Overall survival at 5 years was 77.6% with CapeOx and 74.2% with 5-FU, but the difference was not statistically significant ($P = 0.15$).

Toxicities associated with capecitabine also vary with ethnicity and geographical location; the drug is generally well-tolerated by Asians, and western Europeans have better tolerance than North American patients in terms of reduced incidence of hand–foot syndrome, mucositis and diarrhoea *(14)*. One advantage of the capecitabine-containing regimen is that it obviates the need for long-term intravenous catheter access and the 46-hour infusion associated with the FOLFOX regimen and its variants.

Despite caveats associated with comparisons across phase III trials, the bolus 5-FU and calcium folinate backbone in the NSABP C-07 seems to be the most toxic. Grade 3–4 diarrhoea was noted in 37% of patients receiving 5-FU and oxaliplatin (FLOX) versus 32% of those who received bolus 5-FU and calcium folinate alone *(13)*. By comparison, grade 3–4 diarrhoea was reported in only 11% of individuals who received FOLFOX *(12)* and 19% of those who received CapeOx *(15)*. Overall, the FOLFOX and CapeOx regimens seem to have slightly different but comparable toxic effect profiles, as has been noted in the metastatic setting.

FOLFOX or CapeOx is preferred to FLOX because of the poorer toxicity profile seen with FLOX. Patients with resected stage III colon cancer should receive a fluoropyrimidine alone only if they are not candidates for oxaliplatin (for either medical or financial reasons). Either an infusional 5-FU regimen or an oral fluoropyrimidine, such as capecitabine, for 6 months is preferred to bolus 5-FU and calcium folinate because of lesser toxic effects and, possibly, superior efficacy (for capecitabine).

If a bolus 5-FU and calcium folinate regimen must be chosen for financial or logistic reasons, the RPMI regimen is preferred to the Mayo regimen because of its better haematological toxicity profile.

The health-care systems in some countries may not be able to afford the costs associated with chemotherapy administration and toxicity monitoring and management. For these countries, it should be emphasized that surgical resection alone is potentially curative for stage I, II and III colon cancer. Since patients with early-stage colon cancer are potentially cured with surgery alone, adjuvant chemotherapy should not be administered unless it can be done safely.

Finally, several studies have demonstrated equivalence between low-dose (20 mg/m$^2$) and high-dose (500 mg/m$^2$) calcium folinate when administered with 5-FU *(4)*; the Committee considered that low-dose calcium folinate should be the default recommendation.

*Harms and toxicity considerations*

**Common**

Frequent adverse effects of 5-FU/calcium folinate combination therapy include diarrhoea and associated dehydration, neutropenia (uncommonly leading to infection in <2% of patients), anaemia and mucositis *(12, 16)*. Palmar–plantar erythrodysaesthesia (hand–foot) syndrome is associated with 5-FU and capecitabine, with an increased incidence of up to 60% in patients treated with capecitabine; typically, it resolves following interruption of treatment *(17)*.

Oxaliplatin-containing regimens can lead to sensory neuropathy (24–92% of patients), which is often acute and reversible but may be persistent at high cumulative doses *(11, 12, 14)*. Peripheral neuropathy of greater than grade 2 severity should be managed with dose reduction or delay.

**Serious**

Diarrhoea occurs in up to 50% of patients treated with 5-FU or capecitabine. It can be severe, may require hospital admission for intravenous fluid replacement, and is often dose-limiting *(12, 16)*.

**Recommendations**

Based on the evidence presented in the application, the Expert Committee recommended the addition of capecitabine and oxaliplatin to the complementary list of the Model List of Essential Medicines for the treatment of early-stage (stage III) colon cancer. In addition, the Committee endorsed the use of already-listed calcium folinate and fluorouracil for this indication. The Committee was satisfied that the proposed treatment regimens for stage III colon cancer involving these medicines produce clinically relevant improvements in overall

survival. However, the Committee did not support use of the Mayo clinic regimen of bolus fluorouracil, given that it is associated with greater toxicity than infusional fluorouracil regimens.


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