Early-stage rectal 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 rectal cancer. In addition, the application 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

Early-stage rectal cancer is a potentially curable illness. Surgery is the most critical component of the treatment for this malignancy. Over the past few decades, improvements in surgical technique, specifically the development of the total mesorectal excision (TME), have had a major impact on patient survival. Stage I rectal cancers are curable with surgery alone. The treatment of stages II and III rectal cancer is more complex and should involve a multidisciplinary approach: neoadjuvant chemoradiation with intravenous 5-FU or oral capecitabine is the standard of care for patients with T4 and clinically node-positive disease, and for some patients with T3 disease with low rectal tumours.

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 most common 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, treatment, and monitoring

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 rectal cancer staging, which evaluates the T stage (the extent of spread through the layers that form the wall of the rectum) and N stage (the extent of lymph node involvement) of the tumour, is also important in establishing the degree of loco-regional invasiveness of the tumour. Where available, it is performed by either rectal 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. In developed countries administration is usually performed in outpatient facilities; in other settings, patients may 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 IV 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.

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

Standard neoadjuvant regimens

- **Chemoradiation with 5-FU**
  - continuous infusion 5-FU (225 mg/m^2 per 24 hours) Monday to Friday throughout the course of radiation; or
  - bolus regimen: 5-FU 400 mg/m^2 bolus IV + calcium folinate 20 mg/m^2 IV for four days during weeks 1 and 5 of radiation.

- **Chemoradiation with capecitabine**
  - capecitabine 825 mg/m^2 twice daily Monday to Friday throughout the course of radiation.

Chemoradiation regimens with continuous infusional 5-FU or capecitabine are considered optimal, but bolus 5-FU is a reasonable alternative where the ability to safely deliver infusional 5-FU or capecitabine is not available. No clinical trials have shown superiority of these two options over a bolus regimen but expert opinion and clinical trials data suggest lower toxicity.

The Expert Committee noted that oxaliplatin is not used as part of neoadjuvant chemoradiation for resectable primary rectal cancer.

Standard adjuvant regimens (after neoadjuvant treatment)

- **FOLFOX-6 regimen for 8 cycles (4 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)
  - oxaliplatin 85 mg/m^2 IV on day 1 of each 14-day cycle.

- **CapeOx (3-week cycle; 6 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; 4 months)**
  - 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.

Acceptable regimens where oxaliplatin is unavailable or contraindicated

- **Roswell Park regimen of adjuvant chemotherapy with 4 cycles of 5-FU and calcium folinate (4 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 8 cycles of 5-FU and calcium folinate (4 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 (3-week cycle; 6 cycles–4 months)**
  - capecitabine 1000 – 1250 mg/m^2 twice daily for 14 days of each 21 day-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. If radiation therapy is not available, adjuvant chemotherapy for 6 months is likely to lead to benefits beyond surveillance alone.

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 rectal cancer is a potentially curable illness. Compared with early-stage colon cancer, however, early-stage rectal cancers have a higher risk of local recurrence, and the treatment paradigm has evolved to address this higher risk. Patients with locally advanced rectal cancers receive multidisciplinary care involving surgery, radiation and chemotherapy. In low-income countries, treatment of rectal cancer can be very challenging because of the complexity and the cost of radiation, chemotherapy, imaging and supportive services.

As in colon cancer, surgery is the cornerstone of treatment for early-stage rectal cancer. Locally advanced tumours are removed by either a sphincter-saving low anterior resection or abdominoperineal resection . One of the biggest advances in the treatment of

locally advanced rectal cancer was the development of the total mesorectal excision (TME), which involves a sharp dissection and complete removal of the mesorectum. The TME surgical approach reduces local recurrence rates from 12–25% to 5–6% *(6-8)*. In advanced health-care systems, TME is the standard of care and, given the significant improvement in outcomes, strenuous efforts to adapt this surgical procedure should be made worldwide.

Neoadjuvant chemoradiation was developed to address the high risk of recurrence associated with the disease and, where resources allow, it is the standard of care for patients with stage II or III rectal cancer with T4 and clinically node-positive disease, and for some patients with T3 disease with low rectal tumours. Patients with preoperatively staged tumours that are T1–2/N0 can be treated with surgery alone. Following surgery, if the pathology shows a higher stage, these patients are candidates for postoperative chemoradiation and adjuvant chemotherapy.

The evidence for chemoradiation being effective in the treatment of locally advanced rectal cancer initially came from the GITSG protocol GI-7175 *(9)*. This protocol randomized 227 patients into four groups: surgery alone, postoperative radiation, postoperative chemotherapy, and postoperative chemoradiation. The chemoradiation group had superior overall survival compared with the other groups, and this established chemoradiation as the standard of care *(10)*.

The question of whether chemoradiation should be given before or after surgery was addressed by the German Rectal Cancer Study *(11)*, which found that neoadjuvant chemoradiation improved local control compared with postoperative chemoradiation. There was no survival difference between the two arms. Notably, neoadjuvant chemoradiation increased the number of sphincter-sparing surgeries and had less toxicity than postoperative chemoradiation. The overall five-year survival rates were 76% and 74% respectively (P = 0.80). The five-year cumulative incidence of local relapse was 6% for patients assigned to preoperative chemoradiotherapy and 13% in the postoperative-treatment group (P = 0.006) *(11)*.

The NSABP trial R-04 demonstrated that chemoradiation with capecitabine is equivalent to chemoradiation with 5-FU *(12)*. A German trial corroborated these findings and suggested that capecitabine may be a little more effective than 5-FU *(13)*. Five-year overall survival in the capecitabine group was non-inferior to that in the 5-FU group (76% (95% CI: 67–82) vs 67% (95% CI: 58–74); P = 0.0004; post hoc test for superiority P = 0.05). Three-year disease-free survival was 75% (95% CI: 68–81) in the capecitabine group and 67% (95% CI: 59–73) in the 5-FU group (P = 0.7). Similar numbers of patients had local recurrences in each group (12 (6%) in the capecitabine group vs 14 (7%) in the 5-FU group; P = 0·67), but fewer patients in the capecitabine group developed distant metastases (37 (19%) vs 54 (28%); P = 0.04).

Adjuvant 5-FU based chemotherapy is the standard of care in the developed world for patients who have undergone neoadjuvant chemoradiation. This recommendation is largely based on the successful use of adjuvant chemotherapy in colon cancer *(14-16)*. In addition, a recent trial demonstrated that rectal cancer patients treated with eight cycles of

adjuvant FOLFOX had improved disease-free survival compared with patients treated with eight cycles of adjuvant 5-FU/calcium folinate *(17)*.

As regards use of oxaliplatin as part of FOLFOX or CapeOx regimens in the adjuvant treatment setting, however, the Expert Committee noted that the PETACC-6 study did not show a statistically significant difference in disease-free survival between CapeOx and single-agent capecitabine *(18)*. Results from the German CAO/ARO/AIO-04 trial, which compared bolus 5-FU with FOLFOX, showed a difference in disease-free survival at 3 years of 75.9% versus 71.2% (hazard ratio (HR) 0.79; 95% CI: 0.64–0.98) favouring FOLFOX *(19)*; however, no difference in overall survival was observed between the two groups. In the Phase II ADORE trial, 3-year disease-free survival was 71.6% in the FOLFOX group and 62.9% in the 5-FU + leucovorin group (HR 0.657; 95% CI: 0.434–0.994; $P = 0.047$) *(17)*. Given the variability in the results of these trials regarding the benefit of oxaliplatin-containing treatment regimens, the Committee considered that the evidence was not sufficiently strong to support adjuvant treatment regimens containing oxaliplatin as the standard of care: it is possible that they deliver no additional benefit over 5-FU-based regimens or single-agent capecitabine.

The choice of fluoropyrimidine IV bolus or infusion 5-FU, or oral capecitabine depends upon local experience and the availability of resources. In general, the toxicity of infusion and oral regimens is lower than that of bolus regimens. 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 are diarrhoea and associated dehydration, neutropenia (uncommonly leading to infection in <2% of patients), anaemia, and mucositis *(16, 17, 20)*. 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 (21).

Oxaliplatin-containing regimens such as FOLFOX can lead to sensory neuropathy (24–92% of patients), which is often acute and reversible but may be persistent at high cumulative doses *(16)*. In one study, the FOLFOX regimen caused significant grade 3 neuropathy in 18% of patients *(22)*.

Patients treated with chemoradiation may also experience rectal discomfort and skin breakdown, and female patients are at risk of vaginal stenosis and infertility *(11, 20, 23)*.

Serious

Diarrhoea occurs in up to 50% of patients treated with 5-FU or capecitabine. It can be severe, may require hospital admission for IV fluid replacement, and is often dose-limiting *(16, 20)*.

Recommendations

Based on the available evidence, the Expert Committee recommended the addition of capecitabine to, and endorsed the use of already-listed fluorouracil and calcium folinate on, the complementary list of the Model List of Essential Medicines as neoadjuvant and adjuvant treatment of early-stage rectal cancer.

The Committee did not recommend addition of oxaliplatin to the Model List for this indication. The Committee noted that oxaliplatin is not used as part of neoadjuvant chemoradiation for resectable primary rectal cancer. Additionally, the Committee considered that current evidence was not sufficiently strong to support adjuvant treatment regimens containing oxaliplatin as the standard of care: it is possible that they deliver no additional benefit over fluorouracil-based regimens or single-agent capecitabine.

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