Metastatic colorectal cancer – EML

The application sought endorsement of calcium folinate and fluorouracil, already listed on the complementary list of the Model List of Essential Medicines, for the treatment of metastatic colorectal cancer. The application also sought the addition of oxaliplatin, irinotecan 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

Metastatic colorectal cancer (mCRC) is, with a few exceptions, an incurable illness. Palliative chemotherapy significantly improves survival and provides relief of symptoms in settings with sufficient resources to administer and handle the toxicities of treatment. Multiple chemotherapy regimens are effective. The least costly regimen shown to increase survival is 5-fluorouracil (5-FU)/calcium folinate. The efficacy of 5-FU/calcium folinate is improved, in a usually cost–effective manner, by combining it with oxaliplatin (FOLFOX regimen) or irinotecan (FOLFIRI). It is also thought that first and second lines of treatment should be seen as complementary for reaching maximum benefit from currently available palliative chemotherapy agents. Survival can be further improved, albeit to a small degree, by the first-line use of biological agents such as bevacizumab, cetuximab or panitumumab, followed by other newer agents such as ziv-aflibercept or regorafenib. However, these agents are not usually considered to be cost–effective.

Public health relevance

It has been estimated that worldwide there are 1.2 million new cases of colorectal cancer a year *(1)*. Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and the third in women, causing the deaths of 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 enables 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 usually not feasible in many parts of the world. With poor access to health care added to 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 and testing

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 can be confirmed pathologically.

A critical aspect of evaluating patients with colorectal cancer is establishing whether they have metastatic disease. In high-resource health systems, computerized tomography scan of the chest, abdomen and pelvis is performed routinely. In resource-constrained settings systemic evaluation with less costly abdominal and pelvic ultrasound and a chest X-ray is commonly employed. Preoperative rectal 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 rectal magnetic resonance imaging or endoscopic ultrasound – complex and highly specialized techniques with limited availability in resource-constrained settings.

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

Treatment

Palliative chemotherapy for mCRC has improved in stepwise fashion over the past several decades. Fluorouracil (5-FU) was the first cytotoxic chemotherapeutic agent shown to be effective in mCRC and arguably remains the most efficacious and cost–effective drug against colorectal cancer. Several clinical trials have tested the importance of combining calcium folinate, a reduced form of folate, with 5-FU. A meta-analysis showed that the response rate for 5-FU/calcium folinate is double that for 5-FU alone and also increases survival *(4)*.

An integrated efficacy analysis of two large phase III trials of patients with mCRC showed the oral fluoropyrimidine capecitabine to be equivalent to intravenous 5-FU/calcium folinate in terms of time to disease progression and overall survival (OS) *(5)*.

Subsequent cytotoxic chemotherapeutic agents, irinotecan and oxaliplatin, showed considerable efficacy when added to the 5-FU/calcium folinate backbone. Irinotecan, a type I topoisomerase inhibitor, is combined with 5-FU/calcium folinate in the FOLFIRI regimen. Oxaliplatin, a third-generation platinum compound, is combined with 5-FU/calcium folinate in the FOLFOX (infusional) or FLOX (bolus) regimens or with capecitabine in the CapeOx scheme (also known as XELOX). Multiple clinical trials have shown that the FOLFIRI and FOLFOX or CapeOx regimens are equivalent in terms of efficacy *(6, 7)*. Oncologists typically use one regimen as first-line therapy and then the other as second-line therapy.

Systemic chemotherapy in mCRC is usually not curative. In countries that do not have sufficient resources to administer and handle the toxicities of chemotherapy, it is

appropriate to forgo chemotherapy and focus instead on palliative care. It must also be noted that, where available, multidisciplinary treatment and resection of oligometastatic disease associated with systemic treatment may cure mCRC in some patients.

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 treatment side-effects and should also be monitored and addressed.

Overview of regimens

Standard regimens

Standard chemotherapy regimens for mCRC are used until disease progression or unacceptable toxicity occurs.

- **Modified de-Gramont (2-week cycle)**
  - 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 continuous IV infusion over 46 hours (days 1– 2 of each 14-day cycle)

- **FOLFOX-6 (2-week cycle)**
  - 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 continuous IV infusion over 46 hours (days 1– 2 of each 14-day cycle)
  - oxaliplatin 85 mg/m^2 IV on day 1 of each 14-day cycle

- **FOLFIRI (2-week cycle)**
  - calcium folinate 400 mg/m2 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 continuous IV infusion over 46 hours (days 1–2 of each 14-day cycle)
  - irinotecan 180 mg/m^2 IV on day 1 of each 14-day cycle

- **CapeOx (3-week cycle)**
  - capecitabine 850–1000 mg/m^2 orally twice daily on days 1–14 of each 21-day cycle
  - oxaliplatin 130 mg/m^2 over 2 hours on day 1 of each 21-day cycle

Note: Low-dose calcium folinate, i.e. 20 mg/m^2, may be used instead of higher doses *(8)*. Fixed-dose (50 mg) calcium folinate is also an option.

Alternative regimens

Where administration of 5-FU by continuous infusion or oral capecitabine is not feasible, an alternative regimen is first-line FLOX (using bolus 5-FU) followed by irinotecan on a two- or three-weekly basis as second-line treatment.

- **FLOX (8-week cycle)**
  - 5-FU 400 mg/m^2 IV bolus weekly for first 6 weeks of 8-week cycle
  - calcium folinate 500 mg/m^2 IV weekly for first 6 weeks of each 8-week cycle
  - oxaliplatin 85 mg/m^2 IV on day 1 of weeks 1, 3, 5 of each 8-week cycle

  Note: Low-dose calcium folinate, i.e. 20 mg/m^2, may be used instead of higher doses *(8)*. Fixed-dose (50 mg) calcium folinate is also an option.

- **Irinotecan, single-agent**
  - Schedule 1: 135 mg/m^2 on days 1 and 8 of each 21-day cycle
  - Schedule 2: 180 mg/m^2 on day 1 of each 14-day cycle
  - Schedule 3: 300–350 mg/m^2 on day 1 of each 21-day cycle (this is the least preferred schedule because of toxicity)

Review of benefits and harms

Benefits

Fluoropyrimidines alone

As in the adjuvant setting, fluoropyrimidines form the cornerstone of chemotherapy for advanced disease. Compared with a monthly schedule of low-dose calcium folinate and bolus 5-FU, the modified de Gramont regimen is associated with superior response rates (32% vs. 14%; P = 0.0004) and median progression-free survival (PFS) (28 vs 22 weeks; P = 0.0012); median OS is increased slightly (62 vs 57 weeks; P = 0.067). Grade 3–4 toxic effects were less frequent with the modified de Gramont regimen (11% vs 24%; P = 0.0004) *(9)*.

Similarly, oral fluoropyrimidines such as capecitabine have been compared with 5-FU regimens in several trials, most of which show non-inferiority of oral fluoropyrimidines and, typically, a superior toxicity profile *(5, 10)*.

The choice of fluoropyrimidine (5-FU bolus or infusion or oral capecitabine) should be based on local practice, experience and the availability of infusional capabilities and other supportive treatment. In general, a fluoropyrimidine alone as initial treatment for advanced colorectal cancer should be reserved for patients who are not candidates for more intensive therapy. If a fluoropyrimidine alone is selected, infusional 5-FU or an oral fluoropyrimidine is preferred to bolus 5-FU regimens because of reduced toxic effects and possibly slightly superior outcomes.

Fluoropyrimidine doublets

Oxaliplatin and irinotecan are typically combined with a fluoropyrimidine (irinotecan has single-agent activity, oxaliplatin does not) and have shown good efficacy.

A randomized controlled trial of 387 patients with advanced colorectal cancer compared treatment with 5-FU/calcium folinate with and without irinotecan (the FOLFIRI regimen) *(11)*. Patients in the irinotecan group had a significantly higher response rate than those given 5-FU/calcium folinate alone (49% vs 31%, $P < 0.001$ for evaluable patients; 35% vs 22%, $P < 0.005$ by intention to treat). Similarly, both time to progression (TTP) and OS were greater in the irinotecan group (median TTP 6.7 vs 4.4 months, $P < 0.001$; median OS 17.4 vs 14.1 months, $P = 0.031$).

The FOLFOX regimen (5-FU/calcium folinate plus oxaliplatin) has also been shown to improve response rates and median PFS and OS in patients with advanced colorectal cancer. In the US Intergroup 9741 study – a randomized controlled trial of 5-FU/calcium folinate, irinotecan and oxaliplatin combinations in patients with previously untreated mCRC *(12)* – 795 patients were randomly assigned to receive irinotecan and bolus 5-FU/calcium folinate (IFL), FOLFOX, or irinotecan and oxaliplatin (IROX). Superiority of FOLFOX over the IFL regimen was noted. A median time to progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months were observed for FOLFOX. These results were significantly superior to those observed for IFL for all end-points (6.9 months, 31%, and 15.0 months, respectively, for OS: P = 0.0001; hazard ratio, 0.66) and for IROX (6.5 months, 35%, and 17.4 months, respectively). Significantly lower rates of severe nausea, vomiting, diarrhoea, febrile neutropenia and dehydration were seen with the FOLFOX regimen. Sensory neuropathy and neutropenia were more common with the regimens containing oxaliplatin.

Comparisons of FOLFIRI and FOLFOX have shown similar results for both regimens, in either sequence. A randomized phase III Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) trial showed median survival was 21.5 months in patients treated with FOLFIRI followed by FOLFOX, and 20.6 months in patients treated with FOLFOX followed by FOLFIRI *(6)*. Median second PFS (time from randomization to disease progression after the second line of chemotherapy) was 14.2 months in the FOLFIRI then FOLFOX arm versus 10.9 in the FOLFOX then FOLFIRI arm. In first-line therapy, FOLFIRI achieved 56% response rate and 8.5 months median PFS; FOLFOX achieved 54% response rate and 8.0 months median PFS. Second-line FOLFIRI achieved 4% response rate and 2.5 months median PFS, compared with 15% response rate and 4.2 months PFS for FOLFOX.

A phase III randomized trial comparing FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer observed no difference in overall response rates (31% vs 34%), median time to disease progression (7 months in each arm) or overall survival (14 vs 15 months) between the two treatment groups *(7)*. The authors concluded that both therapies

are effective first-line treatments for advanced colorectal cancer and that the main differences between the two regimens lie in their toxicity profiles.

Substitution of capecitabine for 5-FU has been assessed for regimens containing either irinotecan or oxaliplatin. Non-inferiority of CapeOx over FOLFOX has been noted, with a comparable but different toxicity profile. FOLFOX is associated with more grade 3–4 neutropenia and neutropenic fever, whereas CapeOx causes more grade 3 diarrhoea and hand–foot syndrome.

The FLOX regimen may be used in settings where capecitabine and the ability to administer infusional 5-FU are unavailable, even though it has not been assessed in phase III trials outside the adjuvant setting. Survival is comparable between FOLFIRI and FOLFOX.

Chemotherapy and targeted treatments

Targeted treatments have been investigated extensively in advanced colorectal cancer. Currently, five targeted agents are approved in different jurisdictions for advanced disease: bevacizumab, ziv-aflibercept and regorafenib, which target angiogenesis; and cetuximab and panitumumab, which target the epidermal growth factor receptor . These agents have shown only a small increase in overall survival. For example, in a pooled analysis of seven randomized clinical trials, bevacizumab combined with chemotherapy was shown to increase overall survival by only 2.2 months compared with chemotherapy alone (19.8 months vs 17.6 months) when used in the first-line setting *(13)*. Targeted agents are more expensive than older chemotherapy agents and have not usually been considered to be cost–effective. Therefore, they were not proposed for inclusion in the EML at this time. One set of resource-stratified guidelines, for instance, suggests that 5-FU costs less than US$ 1000 per life-year saved, oxaliplatin or irinotecan can cost up to US$ 40 000 (but probably less nowadays, with the use of generics), and the targeted agents often cost more than US$ 200 000 *(14)*.

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, nausea and vomiting, and mucositis *(15)*. Notably, both FOLFOX and FOLFIRI cause increased myelosuppression and nausea compared with 5-FU/calcium folinate alone.

Palmar–plantar erythrodysaesthesia (hand–foot syndrome) is also common with 5-FU and capecitabine regimens, with an increased incidence of up to 60% in patients treated with capecitabine. This adverse effect typically resolves following interruption of treatment *(16)*. Irinotecan can cause asthenia or weakness and is associated with a cholinergic syndrome characterized by rhinitis, increased salivation, lacrimation, diaphoresis and flushing, although symptoms are typically low-grade.

Serious

Oxaliplatin-containing regimens can cause significant neuropathy, with approximately 18% of patients developing grade 3 neuropathy *(17)*. Irinotecan may cause severe diarrhoea, with approximately 13% of patients developing grade 3–4 events *(11)*. Diarrhoea can be severe with any of the above regimens and may require hospital admission for intravenous fluid replacement. It can be early or late onset and is often dose-limiting *(11, 15, 18)*.

Recommendations

On the basis of the evidence presented in the application, the Expert Committee recommended addition of oxaliplatin, irinotecan and capecitabine to the complementary list of the Model List of Essential Medicines for the treatment of metastatic colorectal cancer. The Committee also endorsed calcium folinate and fluorouracil (already currently included on the complementary list) for use in this indication.

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