The Treatment of Metastatic Colorectal Cancer

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Introduction
Colorectal cancer (CRC) is one of the most common causes of cancer world-wide and is in the Western world one of the most frequent causes of cancer related mortality (1). Approximately 50% of patients with CRC will develop metastases. Most patients with metastatic CRC will die of their disease. Chemotherapy is the basis of the therapy for patients with metastatic CRC. Surgical resection of resectable liver or lung metastases leads to prolonged disease free survival and a 5 year survival of \( \approx 30\% \). Surgery of metastases is unfortunately possible in only a small number of patients.

Cytotoxic Agents in Metastatic Colorectal Cancer

Benefit of palliative chemotherapy
Untreated, patients with metastatic CRC have a median survival of 5 to 6 months. It has been shown in randomized studies that chemotherapy for metastatic colorectal cancer prolongs the survival and maintains or improves the quality of life (2-4). In these trials old 5-FU-based chemotherapy regimens were used. The median survival of the patients treated with chemotherapy was about 12 months compared to 5 to 6 months for the best supportive care groups (2). A Nordic multicentre study randomised asymptomatic patients with advanced CRC to initial chemotherapy with methotrexate, 5-FU and folinic acid rescue for six months or to primary expectancy with chemotherapy only after the appearance of symptoms. Overall survival was significantly longer in the primary chemotherapy group, however observation intervals were relatively long, and more than a third of the observation group never received chemotherapy (3).

Regimens of 5-fluorouracil/folinic acid
5-fluorouracil has been the therapeutic mainstay for colorectal cancer for over 40 years. The major dose-limiting toxicities of the common regimens are mucositis, diarrhoea, plantar-palmar erythema and mild myelosuppression. The standard treatment for CRC for many years was a bolus 5-FU regimen. Several clinical trials, using rigorous definitions of response, suggested that response rate to single agent bolus administration of 5-FU is approximately 10%. Biomodulation of 5-FU with folinic acid (FA), has been shown to increase the activity of 5-FU. Currently, infusional regimens are a better way of administering 5-FU/FA because the response rate is higher, the time to tumour progression is longer, and toxicities are less pronounced (less mucositis, leucopenia, and neutropenia). Median survival rates for infusional regimens are not longer compared to bolus regimens.

New cytotoxic agents
CPT-11 or irinotecan is a camptothecin analogue that inhibits DNA topoisomerase I and induces single strand DNA breaks and replication arrest. Oxaliplatin is a third generation platinum analogue that induces DNA cross linkages and apoptotic cell death. Studies of irinotecan and oxaliplatin in patients refractory to 5-FU have demonstrated the activity of these drugs in second line treatment (4, 5). Two pivotal studies of irinotecan versus best supportive care and of irinotecan versus infusional 5-FU/FA demonstrated a survival benefit for irinotecan in the second line treatment of patients with 5-FU resistant metastatic colorectal cancer (6, 7). The quality of life of patients treated with irinotecan was superior compared to best supportive care and was comparable to the quality of life of patients treated with 5-FU/FA given per infusion.

Studies which compared the combination of 5-FU/FA plus irinotecan and of 5-FU/FA plus oxaliplatin have shown that combination chemotherapy is more active than 5-FU/FA in patients with advanced CRC. In several randomized studies a higher response rate and a longer time to tumour progression or progression free survival were demonstrated for patients treated with 5-FU/FA/irinotecan compared to patients treated with 5-FU/FA only.

The results of clinical studies have demonstrated that combination treatment is more active than 5-FU/FA alone and it is therefore accepted that combination treatment is the standard option in the first line treatment of advanced colorectal cancer. However, these studies don’t answer the question whether all patients should be treated first with a combination regimen of 5-FU/FA/irinotecan or 5-FU/FA/oxaliplatin or with 5-FU/FA only. Further, these studies also showed that although the number of side effects was higher for combination treatment, the side effect pattern was acceptable and manageable and did not influence the patient’s quality of life.

As to treatment regimens for metastatic CRC, a US study compared the IFL regimen (bolus 5-FU/FA + irinotecan) with infusional 5-FU/FA + oxaliplatin (FOLFOX) and with oxaliplatin plus irinotecan in the first line treatment of metastatic CRC. The response rate, time to tumour progression and survival were significantly higher and longer for the FOLFOX regimen compared to the IFL regimen, taking into account the different 5-FU combinations administered in this study (8). Moreover the FOLFOX regimen led to less adverse events. Oxaliplatin/5-FU/FA and irinotecan/5-FU/FA are currently considered as options in the first line treatment of metastatic CRC because they provide similar efficacy but with a different safety profile: oxaliplatin leads to cumulative neurotoxicity and irinotecan can lead to diarrhoea and alopecia.

Oral fluoropyrimidines
It has been shown that the oral fluoropyrimidines are at least as active as intravenous 5-FU (9-13). Three oral fluoropyrimidines have been extensively investigated in colorectal cancer: UFT, eniluracil and capecitabine. UFT is a combination of uracil and tegafur (a prodrug of 5-FU). Tegafur is a normal substrate for dihydropyrimidine dehydrogenase (DPD) and blocks the actions of this enzyme allowing tegafur absorption and the availability of biologically active plasma concentrations of 5-FU. UFT has usually been administered with oral leucovorin (LV = folinic acid). Eniluracil is a direct inhibitor of DPD and is given orally with oral 5-FU; it has, however, been withdrawn from the market due to unacceptable adverse events. Capecitabine is a 5-FU prodrug that can be absorbed through the intestinal mucosa and is converted to 5-FU. Oral fluoropyrimidines are similar in activity to bolus IV 5-FU/FA but are less toxic.
Summary: cytotoxic agents
The summary points on cytotoxic agents as used in the treatment of colorectal cancer are as follows:

• The infused regimens of 5-FU/FA are a more optimal way of administering 5-FU/FA than the bolus regimen.
• Combining two cytotoxic agents is more active in the first line of metastatic CRC than 5-FU/FA alone. The combination of a triple cytotoxic regimen cannot be supported by clinical findings.
• The combination of 5-FU/FA/irinotecan and 5-FU/FA/oxaliplatin have shown similar efficacy in the treatment of metastatic CRC, but with a different safety profile.
• The oral fluoropyrimidines are at least as active as IV 5-FU/FA. Studies have shown similar efficacy of the combination capecitabine and oxaliplatin compared to IV 5-FU/LV/oxaliplatin. The optimal regimen of capecitabine plus irinotecan is still under investigation.
• In patients with metastatic CRC, the three available cytotoxic agents (fluoropyrimidines, irinotecan and oxaliplatin) have been shown to increase overall survival.

Targeted Therapies for Metastatic Colorectal Cancer
Newer biologic agents have entered the clinical arena for the treatment of colorectal cancer. Two targeted therapies have been used in CRC: the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF).

Angiogenesis inhibitors
Bevacizumab
Bevacizumab is a humanized monoclonal antibody that targets and binds to vascular endothelial growth factor (VEGF), thereby inactivating this growth factor before it can bind to its intended receptor. VEGF is a central component in the process of angiogenesis, or the development of new blood vessels. Randomised trials have shown that bevacizumab, when combined with irinotecan plus bolus 5-FU/LV (IFL) in the first-line treatment of metastatic CRC and FOLFOX in second-line treatment, lead to increases in survival, progression-free survival (PFS) and response rate compared to cytotoxic chemotherapy alone (14, 15).

Other studies have shown that bevacizumab enhances efficacy of an active treatment in the first line treatment of metastatic CRC. Treatment with bevacizumab can be continued until disease progression and it can be administered after cytotoxic agents have been discontinued.

The toxicities more commonly associated with chemotherapy, such as nausea, vomiting, diarrhea, cytopenia and asthenia, do not occur as severely with bevacizumab. It should be noted, however, that bevacizumab has no demonstrated activity as a single agent in colorectal cancer. Adverse events associated with bevacizumab are: hypertension, proteinuria, arterial thrombosis, mucosal bleeding (mainly epistaxis), and impaired wound healing. The risk of arterial thrombosis is increased especially in patients over 65 years and in patients with a history of arterial thrombosis (16).

There is currently no evidence to support the use of bevacizumab in the adjuvant setting. Results of studies thus far suggest that the identification of patients who would benefit from a bevacizumab-containing regimen should rely on individual assessment of the likelihood of a patient developing toxicities and on the potential for positive efficacy results.

EGFR inhibitors
Cetuximab
Cetuximab is a chimeric monoclonal antibody that binds selectively to the epidermal growth factor receptor (EGFR). Preclinical studies have indicated that cetuximab had modest in vitro and in vivo single agent activity but had more significant activity when combined with cytotoxic agents.

The BOND trial provided strong confirmatory evidence of the activity of cetuximab in colorectal cancer (17). The response rates were 23% for cetuximab/irinotecan and 11% for cetuximab alone. Because patients in both arms received cetuximab, this trial is in no way an assessment of whether or not cetuximab treatment confers a survival advantage. That question was answered by a trial of the Canadian and Australian groups. These groups showed
that in chemorefractory CRC, cetuximab plus best supportive care (BSC) improves survival compared to BSC alone (18).

Panitumumab and other EGFR-targeting agents
Panitumumab, formally known as ABX-EGF, is a fully humanized monoclonal antibody that also targets the EGFR. A randomized phase III trial of panitumumab plus BSC compared with BSC alone in patients with EGFR-expressing oxaliplatin- and irinotecan-refractory patients showed a significantly longer progression free survival for patients treated with panitumumab (19).

The efficacy and safety of two other EGFR-targeting agents, matuzumab (EMD 72000) and gefitinib, in the treatment of colorectal cancer are currently being investigated in clinical trials.

Challenges with anti-EGFR antibodies
A crucial challenge facing clinicians and researchers is to demonstrate which patients are most likely to respond to bevacizumab-containing regimens and to the anti-EGFR antibodies cetuximab and panitumumab. A second important challenge for the future is to find an answer to the strategic questions: what is the best combination of agents, what is the best sequence of administering these agents, and what is the optimal use of the different cytotoxic agents in combination with various biologicals in CRC.

In terms of treating all types of cancer, an important challenge is to understand more about why tumors that initially respond to a combination of cytotoxics and biologicals may become resistant to this combination. In order to unravel the underlying causes, sequential tumour biopsies and serum and plasma sampling done before, during and after treatment need to be examined for molecular markers that can explain the cause of acquired resistance to the treatment.

The only option to cure patients with metastatic colorectal cancer is the possibility of resection of metastatic disease. Resection of liver-only metastases has become standard practice with long-term survival in 25% to 35% of selected patients. Patients with initially unresectable metastases that are downsized to resectable metastases by systemic treatment have a similar chance of long-term survival after resection (20, 21). For these patients, it is important to determine which combination of cytotoxics and biologicals has the highest likelihood of providing tumour regression that may enhance resection of the metastases. Safety evaluation is very important in this setting since it is actually unclear what the impact of angiogenesis inhibitors will be on postoperative complications and wound healing.

A final challenge is faced by society in general and health economists to discover ways to cope with the rapidly increasing costs of the treatment of metastatic colorectal cancer. Here, identifying which patients will best benefit from which treatment option is crucial.

In conclusion, biologicals have clearly increased the therapeutic options of patients with metastatic colorectal cancer and offer the possibility to prolong survival. The major challenge is now to implement strategies in which patients can be selected, based on molecular characteristics and/or pharmacogenomic profiles, so that the new drugs and the resources available can be used optimally for our patients with metastatic colorectal cancer.

References