

Current status of pharmacological treatment of colorectal cancer

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Abstract

AIM: To review the clinical trials for the development in drugs for chemotherapeutic treatment of colorectal cancer (CRC).

METHODS: A systematic review identified randomized controlled trials (RCTs) assessing drugs for the treatment of CRC or adenomatous polyps from www.clinicaltrials.gov. Various online medical databases were searched for relevant publications.

RESULTS: Combination treatment regimens of standard drugs with newer agents have been shown to improve overall survival, disease-free survival, time to progression and quality of life compared to that with standard drugs alone in patients with advanced colorectal cancer. The FOLFOXIRI regimen has been associated with a significantly higher response rate, progression-free survival and overall survival compared to the FOLFIRI regimen.

CONCLUSION: Oxaliplatin plus intravenous bolus fluorouracil and leucovorin has been shown to be superior

for disease-free survival when compared to intravenous bolus fluorouracil and leucovorin. In addition, oxaliplatin regimens were more likely to result in successful surgical resections. First line treatment with cetuximab plus fluorouracil, leucovorin and irinotecan has been found to reduce the risk of metastatic progression in patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases. The addition of bevacizumab has been shown to significantly increase overall and progression-free survival when given in combination with standard therapy.

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Key words: Colorectal cancer; Metastasis; Chemotherapy; 5-fluorouracil; Leucovorin; Epidermal growth factor receptor inhibitor

Core tip: A systematic review was undertaken to identify randomized controlled trials (RCTs) assessing synthetic drugs for the treatment of colorectal cancer and/or adenomatous polyps from various medical databases, including clinicaltrials.gov, and a total of around 2300 RCTs were screened. After reviewing data from RCTs of synthetic drugs, alone or in combination with biological agents, for the treatment of colorectal cancer, it was concluded that combination regimens of standard chemotherapeutic drugs with new cytotoxic and targeted agents have led to an increase in overall and progression-free survival and have also contributed to increased rates of resectability and improved health-related quality of life in patients.

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INTRODUCTION

Colorectal cancer (CRC) is a malignant neoplasm arising from the lining of the large intestine (colon and rectum). It is the third most common cancer in males and the second in females. Countries such as Australia, New Zealand, Canada, the United States and parts of Europe have the highest incidence rates, whereas China, India, parts of Africa and South America have the lowest risk of colorectal cancer in the world^[1]. This geographical variation in incidence across the world can be attributed to differences in the consumption of red and processed meat, fiber and alcohol as well as body weight and physical activity^[2-7]. However, the incidence of colorectal cancer is increasing in Japan and other Asian countries as there has been a shift towards westernized diets and lifestyles^[2]. The survival rate for colorectal cancer varies with stage of disease at diagnosis and typically varies from 90% for cancers detected at the localized stage to 10% for distant metastatic cancer. The incidence of colorectal cancer has been known to increase with age. The likelihood of colorectal cancer diagnosis increases progressively from a younger age (< 40 years) and rises sharply after the age of 50 years^[8,9]. Several factors such as poor quality diets^[10], lack of physical activity, obesity^[11], cigarette smoking^[12] and heavy alcohol consumption^[13] are associated with an increased risk of colorectal cancer. An individual with a history of adenomatous polyps or inflammatory bowel disease has an increased risk of developing colorectal cancer compared to an individual with no history of either^[12,14].

Colorectal cancer includes malignant growths from the mucosa of the colon and rectum. Cancer cells may eventually spread to nearby lymph nodes and subsequently to more remote lymph nodes and other organs in the body like the liver and lungs, among others. The treatment, prognosis and survival rate largely depends on the stage of disease at diagnosis. Screening for colorectal cancer is particularly effective. Screening can prevent cancer from occurring as it can detect adenomatous polyps that can be successfully removed^[15]. Treatment for colorectal cancer varies by tumor location and stage at diagnosis. Surgical removal of tumor and nearby lymph nodes is the most common treatment for early stage (stage I or II) colorectal cancer. For patients with late-stage disease, chemotherapy alone or in combination with radiation therapy is often given before or after surgery.

MATERIALS AND METHODS

A systematic review was undertaken to identify randomized controlled trials (RCTs) assessing drugs for the treatment of colorectal cancer and/or adenomatous polyps from www.clinicaltrials.gov. Trials with unknown status were excluded. The following electronic databases were searched for RCTs of clinical effectiveness: MEDLINE, Medline In-Process and EMBASE. A separate literature search was undertaken to identify relevant articles from various online databases such as PubMed. The search was

conducted using the following key words and phrases: colon cancer, colorectal cancer, clinical trials and drugs in colon/colorectal cancer.

RESULTS

The search identified 1663 RCTs of synthetic drugs, alone and/or in combination with biological agents, including on-going, completed and suspended/withdrawn/terminated studies in colorectal cancer.

Fluoropyrimidines

Fluoropyrimidines are anti-metabolite agents widely used in the treatment of various cancers. The principal mechanism of action of fluoropyrimidines has been considered to be the inhibition of thymidylate synthase. The response to 5-fluorouracil (5-FU) as a first line monotherapy is low, so it is given in combination with other cytotoxic agents, like oxaliplatin and irinotecan. 5-FU is commonly given either as a bolus injection with leucovorin (folinic acid) or a continuous infusion. While 5-FU bolus treatment favors RNA damage, continuous treatment with 5-FU favors DNA damage^[16]. 5FU when given orally is associated with unpredictable levels in the plasma with extensive interpatient and inpatient variability^[17]. The primary cause of variability in plasma levels is the extensive first pass metabolism of the drug in the gut wall and liver. It was also thought to result from its erratic intestinal absorption due to a difference in concentration of dihydropyrimidine dehydrogenase or DPD (rate-limiting enzyme involved in 5-FU metabolism) in the mucosa. This problem can be overcome by administration of a fluorouracil that is not catabolized by DPD^[18] and the coadministration of oral fluorouracil with an inhibitor of DPD^[19]. Prodrugs of 5-FU are absorbed intact through the gastrointestinal mucosa and undergo enzymatic activation by one or more enzyme systems to release 5-FU intracellularly.

Multi-drug chemotherapy

The Gruppo Oncologico Nord Ovest (GONO) conducted a phase III study involving 244 patients with previously untreated metastatic CRC, comparing fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI). The results of the study demonstrated that the FOLFOXIRI regimen was associated with a significantly higher response rate, progression-free survival and overall survival compared to the FOLFIRI regimen^[20]. In a phase II study of 44 patients with unresectable metastatic colorectal cancer, neoadjuvant chemotherapy with fluorouracil, leucovorin and oxaliplatin (FOLFOX4) was associated with a high response rate, thus allowing for successful resection of disease in a portion of patients^[21].

Oxaliplatin is a diaminocyclohexane platinum compound that acts by impairing DNA replication and induces cellular apoptosis^[22,23]. In the National Surgical Adjuvant Breast and Bowel Project C-07 trial involving 2409 patients, oxaliplatin plus intravenous bolus fluo-

flourouracil and leucovorin was superior for disease-free survival (HR = 0.82; 95%CI: 0.72-0.93; $P = 0.002$) when compared to intravenous bolus fluorouracil and leucovorin. Treatment with oxaliplatin significantly improved overall survival in patients younger than 70 (HR = 0.80; 95%CI: 0.68-0.95; $P = 0.013$), while no positive effect was evident in older patients. In this study, treatment with oxaliplatin in patients > 60 years and females was associated with increased incidence of bowel wall injury^[24]. In another trial involving 2246 patients who had undergone curative resection for stage II or III colon cancer, the rate of disease-free survival at three years was 78.2% (95%CI: 75.6-80.7) in the group given fluorouracil and leucovorin (FL) plus oxaliplatin and 72.9% (95%CI: 70.2-75.7) in the FL group^[25]. In the National Cancer Institute-sponsored trial N9741 involving 1508 patients with locally advanced or metastatic colorectal cancer, oxaliplatin plus fluorouracil and leucovorin (FOLFOX4) was found to be more likely to produce a complete response than treatment with irinotecan plus fluorouracil and leucovorin (IFL) or irinotecan plus oxaliplatin (IROX). In addition, oxaliplatin regimens were more likely to result in successful surgical resections^[26]. However, severe gastrointestinal toxicity and high mortality rates were observed with combination regimens containing daily bolus 5-FU/LV and oxaliplatin or irinotecan^[27].

Irinotecan, a semisynthetic derivative of the natural alkaloid camptothecin, acts by inhibiting the action of topoisomerase I. Although in a previous study combination treatment with irinotecan plus weekly bolus IFL had proven superior to fluorouracil and leucovorin in patients with metastatic CRC^[28], it did not result in a statistically significant improvement in either disease-free or overall survival in patients with stage III colon cancer^[29]. In a phase I / II study involving 23 patients with metastatic colorectal cancer, treatment with capecitabine plus oxaliplatin and irinotecan was well tolerated and the recommended daily dose of capecitabine was 1400 mg/m²^[30].

Capecitabine

Capecitabine, an oral prodrug of doxifluridine (prodrug of 5-FU), is absorbed through the gastrointestinal mucosa^[18]. Oral capecitabine in combination with intravenous irinotecan was an active regimen in a phase II study involving 65 patients with previously untreated metastatic colorectal cancer^[31]. A Dutch Colorectal Cancer Group (DCCG) phase III trial involving 820 patients with advanced colorectal cancer evaluated sequential versus combination chemotherapy with a fluoropyrimidine, irinotecan and oxaliplatin. In the DCCG trial, capecitabine plus irinotecan appeared to be a feasible first-line treatment; however, combination treatment did not significantly improve overall survival compared to the sequential use of cytotoxic drugs in advanced CRC^[32,33]. In a Roswell Park Cancer Institute phase I / II study involving 25 patients with stage II or III rectal cancer, weekly intravenous oxaliplatin with daily oral capecitabine and radiotherapy was associated with a greater rate of pathological responses and demonstrated to be an effective neoadjuvant combi-

nation^[34]. Capecitabine when administered in combination with perifosine showed promising clinical activity compared with single agent chemotherapy in a phase II RCT involving 381 patients with previously untreated metastatic CRC^[35]. Results of a phase II study involving 146 patients with Stage T3 or T4 rectal cancer who received preoperative chemoradiotherapy with capecitabine plus oxaliplatin demonstrated significant clinical activity and acceptable toxicity^[36]. This regimen is currently being evaluated in a phase III randomized trial.

Ftorafur (tegafur) is a prodrug which is coadministered with an inhibitor of DPD (uracil). Coadministration allows for better bioavailability and uniform absorption^[37]. In a RCT of 1608 patients, uracil/ftorafur (UFT) was associated with a higher convenience of care; thus, patients perceived adjuvant treatment with UFT plus leucovorin as more convenient than standard IV treatment with fluorouracil and leucovorin^[38]. However, both therapies achieved similar disease-free and overall survival^[39]. In the adjuvant treatment of 610 patients with stage III colon or rectal cancer, postoperative treatment with UFT was successfully tolerated and improved relapse-free and overall survival in patients with rectal cancer; however, the expected benefits were not observed in colon cancer (HR = 0.89)^[40]. In a phase II RCT involving 58 elderly patients (range, 75 to 90 years) (range, 75 to 90 years) with measurable disease and no prior chemotherapy for metastatic disease, the UFT plus leucovorin regimen was moderately well tolerated and its activity was comparable to intravenous fluorouracil plus leucovorin, although there was increased GI toxicity in most patients^[41,42].

Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR), a 170 kD transmembrane glycoprotein, is a member of the tyrosine kinase receptor family, ErbB. It is known to be overexpressed in malignancies of multiple tissues, including those of the colon, breast, lung and head and neck^[43]. EGFR acts by affecting cell proliferation and survival and therefore has been known to contribute to metastatic progression^[44]. Anti-EGFR therapies include monoclonal antibodies to EGFR and tyrosine kinase inhibitors.

In a multicenter phase II trial of 74 patients with metastatic colorectal cancer, cetuximab seemed to positively interact with oxaliplatin and capecitabine^[45]; however, its correct use in first-line treatment needs to be assessed in phase III trials. In another phase II study of 344 patients with metastatic colorectal cancer, cetuximab in combination with fluorouracil, leucovorin and oxaliplatin (FOLFOX4) demonstrated a higher overall response rate (46% *vs* 36%)^[46] and significantly improved progression-free survival (HR = 0.567, $P = 0.0064$) compared to FOLFOX4 alone^[47]. First line treatment with cetuximab plus fluorouracil, leucovorin and irinotecan was found to reduce the risk of metastatic progression in a Phase III study of 1198 patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases^[48]. A significant increase in resectability was demonstrated by cetuximab in a phase II study of

patients with non-resectable colorectal liver metastases when given in combination with FOLFOX6 or FOLFIRI as neoadjuvant chemotherapy^[49]. Moreover, biweekly cetuximab plus irinotecan as second-line treatment has shown significant anti-tumor activity in patients with irinotecan-refractory metastatic CRC^[50]. Panitumumab, a humanized monoclonal antibody to EGFR, when given in combination with fluorouracil, leucovorin and irinotecan as first-line treatment, has been well tolerated and showed promising activity in patients with metastatic colorectal cancer^[51]. In another phase II study, panitumumab monotherapy was found to be active in Japanese patients with chemotherapy-refractory metastatic CRC^[52]. Immunogenicity of panitumumab when given in combination with oxaliplatin or irinotecan-based chemotherapy was found to be similar to the immunogenicity observed in the monotherapy setting in a phase III study of patients with metastatic CRC^[53].

Although the mechanism of action and safety profile of tyrosine kinase inhibitors such as gefitinib, sunitinib and erlotinib warrant further study in combination with standard regimens, early phase I / II studies showed promising activity and results suggest that they can be safely combined with standard regimens as first-line treatment^[54-57].

Angiogenesis inhibitors

Another strategy to control cell proliferation in malignant tissues is the inhibition of new blood vessel formation. As of now, the main focus has been on inhibiting the protein that stimulates blood vessel proliferation, *i.e.*, the vascular endothelial growth factor (VEGF). The role of bevacizumab, a humanized monoclonal antibody against VEGF, is currently being studied in several randomized trials in the United States and Europe. Bevacizumab, when given in combination with oxaliplatin-based adjuvant therapy, did not prolong disease-free survival and demonstrated a detrimental effect in a phase III study on patients with resected stage III colon cancer^[58]. Although an uncommon occurrence, use of bevacizumab in colorectal cancer has been shown to be associated with an increased risk of bowel perforation and fistula formation that occurs in a small proportion of CRC patients^[59]; however, high dose bevacizumab when administered with IFL was well tolerated and regarded as a highly active regimen in patients with previously untreated CRC^[60]. In a phase II study in patients with previously untreated metastatic CRC, bevacizumab in combination with dose-reduced capecitabine and irinotecan was well tolerated and resulted in favorable outcomes^[61]. In another randomized phase II study of patients with previously untreated metastatic CRC receiving a fluorouracil-based chemotherapy regimen, addition of bevacizumab significantly increased overall and progression-free survival^[62,63].

DISCUSSION

Although during the last decade substantial progress has been made in the diagnosis and successful treatment of

colorectal cancer, clinicians and researchers still face challenges in the detection and management of the disease. Further clarification of the pathology of colorectal cancer at the molecular level may improve treatment options. The ultimate goal of scientists and clinicians in the field of cancer research is aimed not only at long-term survival of patients with this condition but also improvement of health-related quality of life. Pharmacological treatment of colorectal cancer has increased the rate of survival. While incorporation of new cytotoxic drugs and targeted agents has widened the treatment options for patients with metastatic colorectal cancer, combination regimens of standard chemotherapeutic drugs with newer agents have led to an increase in overall as well as progression-free survival. These newer combination regimens have contributed to increased rates of resectability in patients with potentially resectable tumors as well as improved health-related quality of life. Technology has improved the precision of radiation delivery to deep seated tumors. In order to gain the most benefit from these newer chemotherapeutic regimens and technologies, it is imperative to incorporate well-designed, multicenter studies with internationally standardized detection protocols in clinical trials with close collaboration between researchers and clinicians to cope with the vast quantity of data generated.

COMMENTS

Background

This review aims to explore the status of drug regimens, including synthetic drugs alone or in combination with biological agents, available for the treatment of colorectal cancer.

Research frontiers

Several new agents, both synthetic and biological, are currently being studied in clinical trials for their potential as part of the regular drug regimens for treatment of colorectal cancer.

Innovations and breakthroughs

After screening around 2300 randomized controlled trials, the authors found that the newer agents are well-tolerated and their addition to the standard chemotherapeutic drug regimens have led to an improvement in overall as well as progression-free survival in patients with metastatic colorectal cancer.

Applications

This review provides an update on the status of the synthetic drugs and treatment regimens available for the treatment of colorectal cancer.

Terminology

Fluoropyrimidines: Fluoropyrimidines are anti-metabolite agents widely used in the treatment of various cancers that act by inhibiting the enzyme thymidylate synthase. **Angiogenesis:** Angiogenesis is a physiological process of formation of new blood vessels from pre-existing vessels. **EGFR:** Epidermal growth factor receptor, a transmembrane glycoprotein, is a member of the tyrosine kinase receptor family, ErbB.

Peer review

This manuscript is a meta-analysis of current pharmacological treatments for colorectal cancer. The data presented are generally good and may be interesting for clinicians involved in this field.

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