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Review paper

Colorectal cancer—an undertreated disease

Nancy Kemeny
Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA. Tel: (+1) 212 639-8068; Fax: (+1) 212 794-7186.

Surgery is currently the first-line treatment option for primary colorectal cancer (CRC) and resectable metastatic disease. Cytotoxic chemotherapy is used for adjuvant treatment as well as for the treatment of advanced disease; the combination of 5-fluorouracil (5-FU) plus leucovorin is currently the standard chemotherapeutic regimen used in most centers. In many countries patients with CRC do not receive chemotherapy because some clinicians perceive that the benefits of such treatment do not compensate for the potential negative effects on patient quality of life in terms of toxicity and inconvenient dosage schedules. However, recent evidence suggests that the use of cytotoxic chemotherapy can lead to an improvement in quality of life and effective palliation in CRC. A number of new treatment options are becoming available for the treatment of this malignancy. These include new anticancer agents such as thymidylate synthase inhibitors, monoclonal antibodies and topoisomerase I inhibitors, and new treatment methods including hepatic arterial or i.p. chemotherapy, cryosurgery and chemo-embolization. With the increased referral of patients to oncologists and the use of a multidisciplinary team approach, these new agents and new methods of treatment can be fully evaluated for the treatment of CRC, and should ultimately improve the treatment and outcome of this common disease.

Key words: Chemotherapy, colorectal cancer, fluorouracil, leucovorin, thymidylate synthase inhibitors, topoisomerase I inhibitors.

Introduction

Colorectal cancer (CRC) is a common malignancy which is seriously undertreated in many countries despite proven benefits both in the adjuvant and palliative setting. Current data will be reviewed substantiating the hypothesis that CRC is indeed an inappropriately undertreated disease necessitating a re-evaluation of current practice.

CRC is a major health problem with approximately 600 000 new cases diagnosed worldwide each year.[1] Over the last 30 years the incidence of this malignancy has remained relatively constant with approximately 47 cases per 100 000, but there has been a global increase in the total number of cases as a result of population growth.[2]

The majority of colorectal malignancies are thought to develop from pre-existing adenomas through a multistage process involving molecular and subsequent morphological changes.[3] Although the etiology of the disease is complex, a number of risk factors have been identified which include: a history of CRC in a first degree relative,[4] a medical history of chronic inflammatory disease of the gastrointestinal tract,[5] cigarette smoking[6] and a low dietary fiber intake.[7] Considerable research is also in progress to identify the genetic mutations which occur during the development of CRC.[8–10]

A number of effective adjuvant and palliative therapies for the treatment of CRC are now available and several new agents will be introduced into clinical practice in the near future. However, currently in many countries, few patients with this disease receive cytotoxic chemotherapy because of uncertainty regarding its benefits and confusion over which regimen to use; this has a negative effect on patient care and hinders future drug development.

Another treatment option is radiotherapy for rectal cancers, particularly for those patients who are unfit for surgery or who have unresectable tumors. Preoperative radiation therapy and chemotherapy have demonstrated good results with one study demonstrating a 20% complete response rate.[11] Radiotherapy combined with chemotherapy in the adjuvant setting has demonstrated decreased local recurrence and increased survival.[12–15]

At present, surgery is the only treatment option to offer a possible cure for CRC. The surgical procedure involves partial colectomy and regional lymphadenotomy, and may be employed in conjunction with hepatic resection if limited metastatic disease of the liver is present.[16,17] However, the prognosis of many patients following surgery is poor as nearly half of all patients with apparently completely resected CRC ultimately die of metastatic disease.[2]

Chemotherapeutic options

In recent years, the use of chemotherapy to treat early and advanced disease has increased as the benefits of treatment have become apparent. During the last 35 years, 5-fluorouracil (5-FU) has remained the most active single agent for the treatment of CRC despite eliciting response rates of typically less than 20%. To augment the efficacy of 5-FU, oncologists have adopted a number of approaches which include the administration of 5-FU in combination with biochemical modulating agents or other chemotherapeutic agents and the administration of 5-FU by continuous infusion or by hepatic arterial infusion (HAI).

Biochemical modulation

The ability of biochemical agents such as leucovorin, methotrexate and interferon (IFN) to selectively enhance the antitumor activity of 5-FU has been extensively investigated. The most common combination regimen in use today is 5-FU plus leucovorin. In 13 randomized comparative studies of advanced CRC this combination regimen achieved a higher objective response rate in nine studies and an increase in survival in two studies, compared to 5-FU alone.[18–30] A meta-analysis of nine randomized clinical trials involving 1381 patients with advanced CRC also reported a significant improvement in the objective response rate with this combination regimen compared to 5-FU alone (23 versus 11%; OR 0.45; $p < 10^{-7}$), although no significant survival benefit was demonstrated.[31] The modulation of 5-FU appears to be equally effective with high ($\geq$ 500 mg/m^2) and low (20 mg/m^2) doses of leucovorin, although the former is associated with greater toxicity.[24,32]

A number of studies have investigated the efficacy of sequential methotrexate followed by 5-FU. A wide range of response rates have been reported using this approach and a possible reason is the variation in the time interval between the administration of the two drugs. In a review of several studies, the response rate was higher in studies incorporating a time interval of more than 3 h compared to those studies using an interval of only 1 h (26 versus 15%).[33–44] This combination regimen has failed to consistently demonstrate an advantage over 5-FU alone.

Wadler and colleagues originally reported a response rate of 76% for the combination of 5-FU plus IFN-α.[45] However, two subsequent studies failed to confirm this result reporting response rates of 35%[46] and 26%.[47] Excessive neurotoxicity was a problem in the latter study.

Combination therapy

5-FU has been combined with other cytotoxic agents, e.g. methyl-CCNU plus vincristine (MOF) ± streptozotocin or cisplatin. Although some randomized studies evaluating these regimens have reported an increase in response rate, none have demonstrated an increase in survival. Furthermore, this approach is generally associated with increased toxicity and may necessitate a reduction in the total dose of 5-FU administered.[32,48]

Continuous infusion 5-FU

The fraction of colon cancer cells susceptible to bolus 5-FU at any one time is small; colorectal tumors are slow growing with less than 3% of cells dividing at any one time. Furthermore, inhibition of the enzyme thymidylate synthase, following 5-FU bolus administration, is relatively short.[49,50] For this reason continuous infusion of 5-FU has been employed to increase the drug exposure time of the tumor, thereby maximizing the number of tumor cells affected. This approach results in less hematological toxicity compared to bolus administration but may be associated with the development of palmar–plantar erythrodysesthesia. In randomized studies, continuous infusion of 5-FU versus bolus 5-FU has produced increased response rates but has failed to demonstrate any survival benefits.[51–53] This method of administration also incurs greater treatment costs because of the need for infusion devices and infusion ports.

HAI

HAI of 5-FU or its nucleotide derivative, floxuridine (FUDR), permits the direct administration of high doses of drug to the liver without substantially increasing the risk of systemic toxicity. The rationale for this approach is based upon the fact that 15% of all CRC patients[54] and 50–75% of CRC patients with metastatic disease[55] have hepatic involvement. A number of studies have reported significantly higher overall response rates and in some cases even an improvement in overall survival with HAI compared to systemic infusion.[55] In more recent studies using

the 5-FU analog FUDR plus leucovorin or FUDR plus dexamethasone, response rates as high as 70% and median survival times of 28 and 23 months, respectively, have been reported.[55,56] Two European studies have shown an increase in survival[57,58] and in one an increase in quality of life[58] with HAI versus systemic chemotherapy. Toxicities include liver and bile duct damage and gastrointestinal hemorrhage.[32] The Cancer and Leukaemia Group B study group (CALGB) is currently conducting a large randomized study to compare systemic chemotherapy with HAI and this will hopefully answer the question of whether HAI does actually increase survival.

Adjuvant chemotherapy

The improvements in response rate achieved with biochemical modulation of 5-FU in advanced disease have been translated into real survival advantages in the adjuvant treatment of CRC. Several studies have demonstrated that adjuvant chemotherapy for Dukes stage C disease is associated with a survival advantage compared to surgery alone.[15,59–62] The ability of levamisole to enhance the efficacy of 5-FU in the adjuvant treatment of colorectal cancer was reported by Moertel in 1990[63] and led the National Institute of Health (NIH) to issue a consensus statement in April 1990 recommending the use of 5-FU plus levamisole as adjuvant therapy for Dukes stage C disease.[2] More recently, Moertel and colleagues published the results of a 5-year follow-up study.[62] They concluded that the combination of 5-FU plus levamisole as adjuvant therapy in this setting can reduce the recurrence rate by 40% ($p < 0.0001$) and the death rate by 33% ($p = 0.0007$) compared to observation alone. However, several workers have queried the role of levamisole as adjuvant therapy.[64,65]

There is some evidence to suggest that leucovorin increases the efficacy of 5-FU in this setting. In a recent pooled analysis of data from three independent trials, involving over 1400 patients, the investigators reported a significant reduction in the risk of recurrence (35%; $p < 0.0001$) and death (22%; $p = 0.029$) with the combination regimen of 5-FU plus leucovorin compared to surgery alone.[61]

Current issues

Although encouraging results have been achieved in clinical studies, many clinicians believe that the benefits of chemotherapy do not compensate for the negative impact on quality of life. However, recent data suggests that the use of chemotherapy to treat advanced CRC can in fact lead to an improvement in quality of life and palliative benefits.[66–68] Furthermore, studies comparing chemotherapy to supportive care alone[58,66,68] and early chemotherapy to no chemotherapy until symptom development[69] have reported an improvement in survival of approximately 5–6 months. The overall cost for early intervention was also shown to be comparable to that of no treatment or delayed chemotherapy suggesting that the use of chemotherapy is in fact cost-effective.[67,68]

The vast array of 5-FU plus leucovorin combination regimens currently used worldwide (Table 1) and a lack of conclusive data to demonstrate the overall advantage of one specific regimen may also have contributed to undertreatment of CRC. Moreover, clinical studies in the field of CRC have undoubtedly been hampered by the low number of patients participating in clinical trials. Only 1% of patients with advanced disease enter clinical trials,[70] which is surprising in view of the benefits demonstrated with chemotherapy in clinical studies and the general willingness of patients to receive treatment.[71]

Limited information is available regarding the percentage of patients with CRC referred to oncologists from surgeons, but it is probable that the low number of patients participating in clinical trials is primarily due to low referral rates. In a recent study which analyzed the pattern of referral for CRC from the surgeon to the oncologist, 555 patients were considered to have had curative surgery but only 4% were referred and of a further 179 patients who received palliative surgery, only 22% were subsequently referred.[74] In a more recent survey of 133 patients who had undergone surgery for CRC, a similar low referral rate was observed;[75] only 13% of patients with Dukes stage B and 30% of patients with Dukes stage C disease were referred for adjuvant chemotherapy.

Although the benefits of adjuvant and palliative chemotherapy have been clearly demonstrated the real impact will only be realized after more patients have participated in clinical trials. An important example of this is in the field of breast cancer. The benefits of chemotherapy in this disease were identified only after tens of thousands of patients had entered clinical trials[76–78] and this enabled the optimal chemotherapy regimen for the treatment of breast cancer to be determined.

Table 1. Combination regimens of 5-FU plus leucovorin (LV) frequently used in the treatment of colorectal cancer

Regimen	Drugs	Dose	Duration (days)	Frequency
Mayo[25]	5-FU	425 mg/m^2/day i.v.	1–5	every 28–35 days
	LV	20 mg/m^2/day i.v.	1–5	
Machover[72]	5-FU	370–400 mg/m^2/day i.v.	1–5	every 28 days
	LV	200 mg/m^2/day i.v.	1–5	
City of Hope[27]	5-FU	370 mg/m^2/day i.v.	2–6	every 28 days
	LV	500 mg/m^2/day i.v. infusion over 24 h	1–5.5	
Roswell Park Cancer Institute[18]	5-FU	600 mg/m^2/day i.v.	1	every 7 days
GITSGa/Genova[21,24]	LV	500 mg/m^2/day i.v. infusion over 2 h	1	
Bologna[19]	5-FU	600 mg/m^2/day i.v.	1	every 7 days
	LV	200 mg/m^2/day i.v.	1	
De Gramont[73]	LV	200 mg/m^2/day i.v. infusion over 2 h then	1 and 2	every 14 days
	5-FU	400 mg/m^2/day i.v. bolus then	1 and 2	
	5-FU	400 mg/m^2/day i.v. infusion over 22 h	1 and 2	
Nordicb (FLv)[67]	5-FU	500 mg/m^2/day i.v. bolus	1 and 2	every 14 days
	LV	60 mg/m^2/day i.v. bolus	1 and 2	

[a]Gastrointestinal Tumour Study Group.
[b]Methotrexate and other cytotoxic agents are sometimes used in combination with this regimen.

Future developments

Inhibitors of topoisomerase I and thymidylate synthase as well as monoclonal antibodies are currently the most promising areas of new drug development in the field of CRC. Several topoisomerase I inhibitors are currently in development, including topotecan, GG 211 and CPT-11. DNA topoisomerase enzymes reduce the torsional forces imposed upon supercoiled DNA during replication by introducing single-strand DNA breaks. This subsequently permits progression of the replication fork enabling DNA replication and transcription to proceed.[79] Although topotecan has little activity in CRC, CPT-11 has demonstrated useful activity in this setting. In a large multicenter trial, CPT-11 was associated with an overall response rate of 18% which was similar in previously untreated patients (18.8%) and those who had received prior chemotherapy (17.7%).[80] However, a response rate of 32% has been reported in one study of previously untreated patients.[81]

Considerable research has focused on the development of thymidylate synthase inhibitors. The objective of this approach has been to produce direct and specific inhibitors of this enzyme with an improved safety profile compared to that of 5-FU, which is a thymidylate synthase inhibitor with non-specific inhibitory activity against RNA. Several compounds are currently being evaluated including classical antifolates such as LY 231514 and ZD1694 (Tomudex®) as well as non-classical antifolates AG 331 and AG 337. Most of these agents are in the early phase of clinical development, however, with phase III trial results reported recently,[82] Tomudex® is the closest to becoming available for widespread clinical use. Tomudex® is associated with a convenient administration schedule and has demonstrated promising activity in the first-line management of advanced CRC. Furthermore, phase III investigations have demonstrated a lower incidence of leucopenia and mucositis with Tomudex® compared to the conventional combination regimen of 5-FU plus low-dose leucovorin (Mayo regimen).[83]

17-1A is a mouse IgG2a antibody which recognizes tumor-associated antigens expressed by CRC cells. Once bound to a tumor cell it causes cell death by invoking the host to produce an immune response to the cell. Although 17-1A has no activity in advanced disease, it has demonstrated some activity in the adjuvant setting.[84]

Although CRC is a common malignancy it remains an undertreated disease in many countries. This is despite the publication of several studies demonstrating the benefits of chemotherapy when used in the adjuvant or palliative setting. There is a need for the introduction of new anticancer agents with greater efficacy, improved tolerability and more convenient administration schedules. It is anticipated that with the introduction of new anticancer agents the prognosis and quality of life of patients with this disease may improve. However, this will only be achieved with greater patient referral by surgeons to oncologists for adjuvant or palliative chemotherapy and the use of a multidisciplinary team approach in patient care.

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