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Review paper

Continuing the fight against advanced colorectal cancer: new and future treatment options

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The benefit of chemotherapy in the treatment of advanced colorectal cancer has now been clearly demonstrated with several studies reporting advantages in terms of overall survival, quality of life and effective palliation following chemotherapy plus supportive care in comparison to supportive care alone. However, the survival benefit achieved with the current 5-fluorouracil (5-FU)-based regimens is modest and thus investigations are ongoing to identify more effective agents with novel mechanisms of action. The three new agents likely to have the greatest impact in the near future are the thymidylate synthase inhibitor ZD1694 (Tomudex®), the topoisomerase I inhibitor irinotecan (Campto®) and the new platinum compound, oxaliplatin (L-OHP®). Promising response rates of 26 and 20% have been reported with ZD1694 in patients with advanced colorectal cancer in phase II and III studies, respectively. In a European phase II study, irinotecan has achieved response rates of 19% in chemotherapy-naïve patients and 18% in pretreated patients with advanced disease. Oxaliplatin has mainly been investigated in combination with continuous infusion 5-FU, with response rates of 29–58%. Other agents currently in development include monoclonal antibodies (e.g. 17-1A and MN-14), protein synthesis inhibitors (e.g. RA 700) and angiogenesis inhibitors (e.g. PF 4). [© 1998 Rapid Science Ltd.]

Key words: Colorectal cancer, fluorouracil, irinotecan, oxaliplatin, treatment outcome, ZD1694.

Introduction

In industrialized countries, colorectal cancer is the third most common malignancy after lung cancer and prostate cancer in men, and breast cancer in women. In Europe in 1990, there were approximately 170 000 new cases and over 90 000 deaths due to the disease.[1]

Although surgery is currently the first-line treatment for colorectal cancer, surgical cure is not possible in approximately 40% of patients because of the advanced stage of their disease;[2] whereas, if diagnosed at a very early stage, colorectal cancer is associated with an excellent prognosis following primary surgical resection. The 5-year survival rate for patients with tumors involving only the mucosa or submucosa is in excess of 90%.[3] For more advanced stages, adjuvant chemotherapy following 'curative' resection has been shown to have a significant impact on survival in patients with Dukes stage B_2 or C disease, with reported 5-year survival rates of 89 and 65–69%, respectively.[4–6]

Unfortunately, approximately 10–25% of patients ultimately develop local recurrence at the primary tumor site following potentially curative surgery,[7] and although some reports suggest a high rate of resectability for recurrent disease,[8,9] the frequent occurrence of disseminated disease often makes cure impossible. For patients with advanced disease localized in the liver, hepatic resection has been associated with 5-year survival rates of approximately 25%.[10,11] However, for the majority of patients with advanced disease not amenable to surgery, palliative chemotherapy is the most appropriate treatment option.

It is only recently, following the publication of several small but important clinical studies, that the benefit of cytotoxic chemotherapy in the treatment of advanced disease has been realized. Early chemotherapy in patients with asymptomatic advanced disease has been shown to be beneficial in terms of survival (14 versus 9 months; $p<0.02$), time to disease progression (8 versus 3 months; $p<0.001$) and time to symptom development (10 versus 2 months; $p<0.001$) compared with chemotherapy delayed until the onset of symptoms.[12] Scheithauer and colleagues also reported a doubling of survival (11 versus 5 months; $p=0.006$) and quality-of-life benefits with chemotherapy plus supportive care compared with supportive care alone.[13] Similar results were reported

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by Glimelius and colleagues: chemotherapy plus supportive care produced a doubling of survival (12 versus 6 months) and a favorable quality-of-life outcome was reported in 58% of patients, compared with only 29% of patients in the best supportive-care group ($p < 0.05$).[14]

Current chemotherapeutic options for advanced colorectal cancer

The non-specific thymidylate synthase (TS) inhibitor 5-fluorouracil (5-FU) has remained the mainstay of chemotherapy for the treatment of advanced colorectal cancer since its introduction into clinical practice in the 1950s. However, in view of the low response rates typically achieved with 5-FU bolus monotherapy (approximately 10%),[15] several alternative 5-FU-based therapeutic strategies have been investigated.

To date the most widely adopted regimen is the combination of 5-FU with the biochemical modulating agent folinic acid (leucovorin).[16] This selection has been made on the basis of a large number of trials that have reported benefits in terms of response rate and, to a lesser extent, survival with 5-FU plus folinic acid compared with 5-FU alone. A recent meta-analysis of nine clinical studies evaluating the efficacy of various regimens of 5-FU plus folinic acid reported a doubling in the response rate compared with 5-FU monotherapy (23 and 11%, respectively; odds ratio 0.45; $p < 10^{-7}$).[15] In addition, Poon and colleagues reported a significant prolongation of survival (approximately 5 months; $p = 0.05$) and quality-of-life benefits (performance status, weight gain and symptomatic relief) ($p < 0.05$) with this regimen compared with 5-FU monotherapy.[17]

The biochemical modulation of 5-FU by methotrexate also demonstrated superiority to 5-FU alone in terms of response rate (19 versus 10%; $p < 0.001$) and, to a lesser extent, survival (10.7 versus 9.1 months; $p = 0.024$) in a recent meta-analysis ($n = 1178$).[18] However, this combination regimen is currently less popular than the standard regimen of 5-FU plus folinic acid.

Other chemotherapeutic approaches evaluated for the treatment of advanced colorectal cancer include the administration of high doses of 5-FU by continuous infusion or the combination of 5-FU with other cytotoxic agents. Continuous infusional therapy has been investigated in an effort to maximize the number of cancer cells likely to respond to the cytotoxic action of 5-FU. Although an improvement in response rate has been demonstrated with continuous versus bolus therapy,[19,20] no clear survival benefit has been demonstrated. With regard to polychemotherapy, there is a lack of conclusive data to suggest that any of the combination regimens of 5-FU with, for example, cisplatin[21,22] or methyl-CCNU plus vincristine[23–25] are superior to 5-FU alone. This approach is also generally associated with increased toxicity and may require a reduction in the dose of 5-FU administered.

More recently, a number of investigators have utilized locoregional therapy in the treatment of colorectal hepatic metastases. Floxuridine, a derivative of 5-FU which undergoes extensive first-pass metabolism, is the most extensively used chemotherapeutic agent in this setting, with promising results having been reported in terms of both response rate (42–50%)[26,27] and survival (median survival 13.5–15 months).[28,29] However, this procedure is still in the investigational stage, and the severe toxicity frequently associated with this technique (chemical hepatitis and biliary sclerosis) and the need for expensive infusion pumps currently limits the utility of this approach.

Thus, although advances have been made in the treatment of advanced colorectal cancer with 5-FU-based treatments, the survival benefit achieved is typically modest and for this reason clinical studies are still ongoing to identify more effective treatment regimens. In this continued search, many research departments are focusing their efforts on the development of new chemotherapeutic agents with novel mechanisms of action distinct from that of 5-FU. Numerous examples of such agents are in various stages of development for the treatment of colorectal cancer and the remit of this article is to provide a broad overview of some of the compounds that should have a considerable impact on the future treatment of advanced disease.

New and future treatment options for advanced colorectal cancer

Topoisomerase I inhibitors

The nuclear enzyme topoisomerase I is essential for relaxing supercoiled double-stranded DNA, thus enabling DNA transcription and translation to proceed. This is achieved by forming a covalent adduct between topoisomerase I and DNA, termed a 'cleavable complex'. This covalent topoisomerase I-DNA complex induces a transient single-strand break in the DNA backbone through which the intact strand can pass, facilitating the transcription and translation of the genetic material; the nicked strand is subsequently resealed. Topoisomerase I inhibitors reversibly stabi-

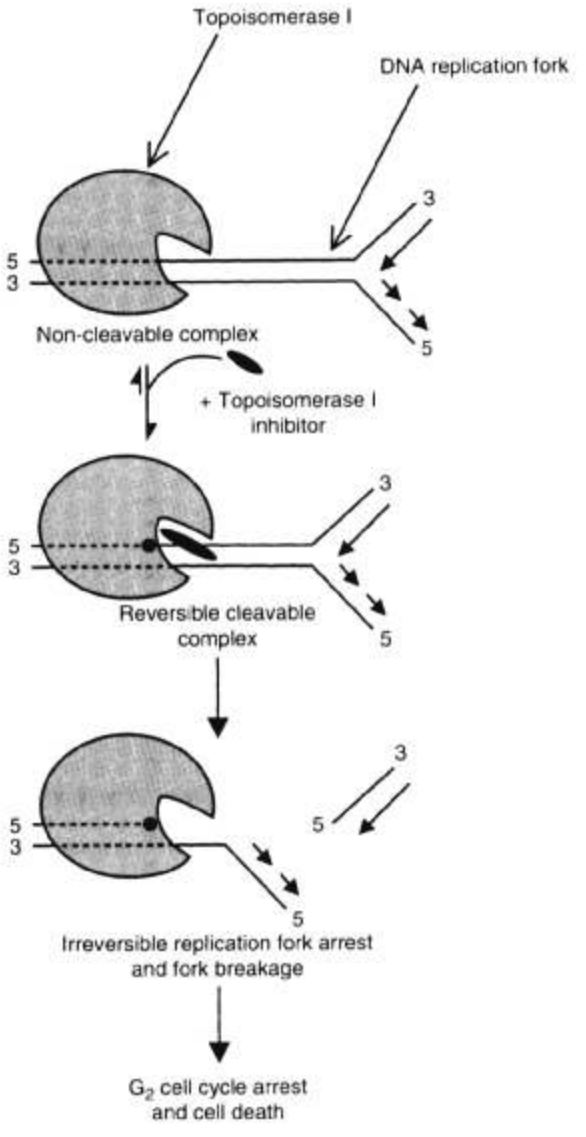

Figure 1. A fork collision model for topoisomerase I inhibitor drugs. (Reproduced, with permission, from the *Annual Review of Pharmacology and Toxicology*, **34**, ©1994, by Annual Reviews Inc.)

lize this cleavable complex, and the resulting collision between this cleavable complex and the moving DNA replication fork is the principal cause of their cellular cytotoxicity (Figure 1). This results in the formation of double-strand DNA breaks and leads to the arrest of the cell cycle, predominantly in the S phase.[30,31] The high intracellular levels of topoisomerase I in some tumor cells (e.g. colon cancer cells) relative to normal tissue[32] makes this enzyme a rational target for the development of novel anticancer agents.

Camptothecin, an alkaloid extract of the plant *Camptotheca accuminata*, was the first topoisomerase I inhibitor to be isolated. In the early 1970s the efficacy of camptothecin was evaluated. However, despite promising activity against several experimental tumor models,[33,34] camptothecin was found to be associated with excessive toxicity, including myelosuppression and hemorrhagic cystitis. This led to the cessation of further development of the drug. An investigational program was subsequently pursued to develop structurally related compounds with greater antitumor activity and reduced toxicity, and this resulted in the identification of a number of active analogs, including irinotecan (Campto®), GG211 and 9-AC.

Irinotecan (Campto®). Irinotecan is a semi-synthetic water-soluble derivative of camptothecin that is converted by the carboxylesterase enzyme *in vivo* to the active metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38).[30] The efficacy of single-agent irinotecan as both first- and second-line treatment for advanced colorectal cancer has been evaluated in phase II studies in over 300 patients. Four phase II studies have been conducted in Japan and the USA using a variety of administration schedules: 100 mg/m^2 once weekly or 150 mg/m^2 once every 2 weeks in Japan[35] and 125 mg/m^2 weekly for 4 weeks followed by a 2-week rest in the USA.[36–38] Response rates of 15–32 and 22–25% were reported in chemotherapy-naïve and pretreated patients, respectively.

The pivotal phase II study conducted in Europe evaluated an irinotecan dosage of 350 mg/m^2 administered once every 3 weeks. Response rates were comparable in both the chemotherapy-naïve (n = 48) and pretreated (n=130) eligible patient groups: 18.8% (95% CI: 8.9–32.6) and 17.7% (95% CI: 11.5–25.5), respectively.[39] A response rate of 16.1% (95% CI: 8–27.6) reported for 62 eligible patients who had progressed while on previous 5-FU-based chemotherapy was suggestive of a lack of cross-resistance between 5-FU and irinotecan. In both the pretreated and chemotherapy-naïve patient groups, the median duration of response was 9.1 months (range 1.6–17).

Although not cumulative, 47% of patients experienced grade 3/4 neutropenia in the European study and febrile neutropenia was reported in 15% of patients.[40] The administration of irinotecan is also frequently associated with the development of two different types of diarrhea: an early type which can be controlled by anticholinergic therapy and a delayed type which appears to be predominantly secretory[41] and can lead to severe dehydration if not promptly treated. In a European phase II study, delayed diarrhea developed in 87% of patients (grade 3/4 in 39%)[40] and high-dose loperamide was reported to be the best supportive treatment. Preventive treatment with the

enkephalinase inhibitor acetorphan alone[42] or in combination with loperamide[43] has also demonstrated some utility in this setting. However, the development of delayed diarrhea may present a potentially significant barrier to the widespread use of irinotecan in clinical practice. The results of ongoing clinical studies will help further define the role of irinotecan in the treatment of advanced colorectal cancer.

Topotecan. Topotecan is currently in phase III clinical development and has demonstrated promising activity in a number of cancers, including breast and small cell lung cancer. However, a recent phase II study evaluating a topotecan infusion of 1.5 mg/m^2 per day for five consecutive days every 3 weeks reported no objective response among 19 enrolled patients with colorectal cancer.[44]

GG211. In vitro GG211 was 2.3- to 4.3-fold more potent than topotecan in inhibiting topoisomerase I.[45] Furthermore, short bolus administration and protracted infusion schedules of GG211 were 1.5- to 1.8-fold more active than topotecan in suppressing the tumor growth of a number of cancer cell lines, including SW-48 colon tumors. In a phase I study, objective clinical responses have been reported with GG211 in colorectal, breast and ovarian cancer,[46] and the drug is now undergoing phase II investigations.

Other topoisomerase I inhibitors. Other topoisomerase I inhibitors in development include: 9-aminocamptothecin (9-AC) in early phase I trials in the USA; GI147211A, which is in phase II development and has been shown to inhibit the growth of HT-29 and SW-48 colon tumors;[45] and DX8951, which is still under preclinical development.

TS inhibitors

The development of direct and specific inhibitors of the enzyme TS has recently been the focus of considerable interest. This enzyme is essential for DNA synthesis and, in conjunction with the co-factor 5,10-methylene tetrahydrofolate, converts the substrate deoxyuridine monophosphate (dUMP) to thymidine 5′-monophosphate (dTMP). dTMP is subsequently metabolized to thymidine 5′-triphosphate (dTTP), which is essential for DNA replication and repair.

The unique specificity of TS to DNA formation makes this enzyme an attractive target for the development of anticancer agents as the theoretical incidence of unwanted toxicities related to the interference with other biochemical pathways, such as RNA synthesis, should be minimal. However, in practice this argument is dependent upon the specificity of the TS inhibitor. 5-FU is an indirect TS inhibitor that requires prior conversion to active metabolites (most importantly FdUMP) (Figure 2). This indirect mechanism of action results in non-specific effects on purine and RNA synthesis, which is considered to contribute markedly to the toxicity profile of the drug.[47] In the search for compounds with improved toxicity profiles, researchers have therefore focused their efforts on the development of specific, direct inhibitors of TS, several of which are currently in development for the treatment of colorectal cancer.

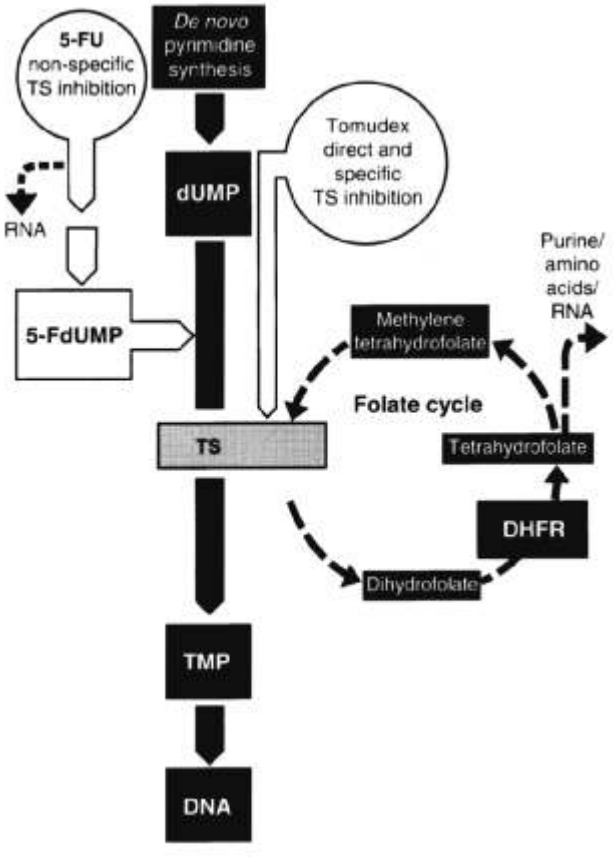

Figure 2. The different methods of inhibition of TS by ZD1694 and 5-FU.

ZD1694 (Tomudex®) The quinazoline folate analog ZD1694 is a direct, specific TS inhibitor currently undergoing a phase III evaluation as single-agent, first-line therapy for advanced colorectal cancer. ZD1694 is taken up into the cells via the reduced folate membrane carrier system and then extensively polyglutamated to more potent forms.[48] Polyglutamation

extends the intracellular retention of ZD1694 and prolongs TS inhibition, permitting the use of a single-dose schedule once every 3 weeks.[48]

To date, ZD1694 has demonstrated promising clinical activity in the treatment of advanced colorectal cancer in two large clinical studies (phase II and phase III).[49,50] Both studies evaluated the efficacy of ZD1694 (3 mg/m^2) administered as a 15 min i.v. infusion once every 3 weeks in patients with advanced or metastatic disease. Prior palliative treatment with chemotherapy was not allowed. Objective response was assessed using WHO/UICC criteria as recommended by the US National Cancer Institute (50% or greater reduction in tumor size).

A total of 176 patients were enrolled in the phase II study and objective responses (four complete and 41 partial responses) were reported in 26% of patients (95% CI: 19–33%) with a median duration of 5.7 months.[49] Median time to disease progression was 4.2 months and median survival 9.6 months. The subsequent phase III study compared the efficacy and tolerability of ZD1694 with the Mayo Clinic regimen of 5-FU (425 mg/m^2) plus low-dose folinic acid (20 mg/m^2) for five consecutive days every 4–5 weeks.[50] A total of 439 patients were randomized to treatment, and objective response rates of 20 and 13% were reported in the ZD1694 and 5-FU/folinic acid cohorts, respectively (odds ratio: 1.7; 95% CI: 0.98–2.81; $p = 0.059$). There was no statistically significant difference in time to disease progression between the two treatment groups.

Quality-of-life issues were also addressed in the phase III study using the validated standard quality-of-life questionnaire developed by the European Organization for the Research and Treatment of Cancer (EORTC).[51] Although no overall difference in patient well-being was demonstrated between those patients treated with ZD1694 or 5-FU/folinic acid, both groups experienced an improvement in terms of emotional function, sleep disturbance, pain and global quality of life. ZD1694 also demonstrated palliative benefits [improved performance status (34 versus 25%) and weight gain (15 versus 12%)] at least as frequently as the comparative Mayo regimen.

ZD1694 may also offer advantages over 5-FU in terms of tolerability. In the phase III study, ZD1694 was associated with a significantly lower incidence of both severe (grade 3/4) leucopenia (10 versus 26%) and mucositis (2 versus 22%) ($p < 0.001$) compared to treatment with 5-FU/folinic acid. The incidence of increased liver transaminases was significantly higher in the ZD1694 cohort (10 versus 0%; $p < 0.001$), but this effect was generally self-limiting and asymptomatic. Other frequent adverse effects included diarrhea, which developed in 13 and 11%, and nausea and vomiting, which developed in 12 and 9% of ZD1694- and 5-FU/folinic acid-treated patients, respectively. Of note, 74% of patients receiving ZD1694 and 52% receiving 5-FU/folinic acid were able to receive their treatment on time without significant dose reduction or delay. The administration of ZD1694 was not associated with the development of severe delayed diarrhea.[50]

In view of the promising clinical results reported with ZD1694 to date, the results of ongoing phase III studies are awaited with interest.

LY231514. LY231514 is currently in phase II clinical development for the treatment of patients with colon cancer. In preclinical studies LY231514 was highly active in murine tumor models and completely suppressed tumor growth in two human colon xenografts.[52,53] Several responses were observed in cancer patients in phase I studies. A phase II trial in patients with colon and pancreatic cancer is underway.

AG331 and AG337. The lipophilic compounds AG331 and AG337 cross the cell membrane by passive diffusion. In preclinical studies, AG331 killed a range of tumor cells, including thymidine kinase-deficient human colon adenocarcinoma, and the drug is now in phase I of clinical development.[54] The 5-substituted quinazoline AG 337 is currently in phase II trials in patients with colon cancer.

ZD9331. ZD9331 enters the cells via the reduced folate carrier, but unlike ZD1694 it does not undergo polyglutamation and is therefore not retained intracellularly in a polyglutamated form for prolonged periods. In preclinical studies, ZD9331 was active against a number of human tumor xenografts, including Colo205 and Colorectal LoVo.[55] The drug is still in preclinical development.

BW1843U89. A phase I trial has also commenced recently with the benzoquinazoline folate analog, BW1843U89. This agent was found to destroy WiDr human colon carcinoma spheroids in preclinical studies[56] and to be active against various tumor xenografts in animal models.

Oxaliplatin

Oxaliplatin (*trans*-l-diamino cyclohexane) (L-OHP) is a non-nephrotoxic third-generation platinum complex in clinical development. It causes minimal hematolo-

gical toxicity, and the dose-limiting toxicity of the drug is a peripheral and/or pharyngo-laryngeal dysesthesia caused and aggravated by the cold. This effect is dose dependent in terms of duration and intensity, and may in some cases cause functional impairment which is generally reversible on discontinuation of treatment.[57] In a phase II study, 29 patients with metastatic colorectal cancer were treated with a 5-day chronomoduated continuous infusion of oxaliplatin 30-40 mg/m^2. Adverse events were peripheral sensory neuropathy (84% of courses), mild nausea and vomiting (61%) which required no antiemetic medication in 81% of courses, and diarrhea (43%). No renal or audiotoxicity developed and hematological toxicity was minimal.[58]

In small phase II studies, oxaliplatin has demonstrated promising activity as a modulator of 5-FU activity in the treatment of advanced colorectal cancer. Studies have been conducted using a combination of 5-FU, folinic acid and oxaliplatin, administered mostly using a chronomodulated continuous infusion schedule. Using this regimen, response rates between 29 and 58% have been reported for first- and second-line treatment.[59-63] However, far lower response rates (10.4%) have been reported with oxaliplatin monotherapy in this setting,[64] further endorsing the 5-FU-modulatory activity of oxaliplatin.

Phase III trials comparing 5-FU and folinic acid with or without oxaliplatin are currently underway.

Monoclonal antibodies (mAb)

Recently, considerable interest has been focused on the development of mAb for the treatment of colorectal cancer. This has been instigated following the identification and characterization of a number of tumor-associated antigens (TAAs) on the surface of colorectal cancer cells that are undetectable or down-regulated on non-cancerous cells. By developing mAb to target specific TAAs, e.g. CO17-1A or carcinoembryonic antigen (CEA), host defense mechanisms are activated; unconjugated mAb promote a number of immune mechanisms, including antibody-dependent and/or complement-dependent cytotoxicity,[65] which ultimately lead to cell death.

A number of mAb are currently in clinical development, but the most extensively investigated is mAb 17-1A (mouse IgG2A). This is a murine mAb which targets the CO17-1A antigen expressed on colorectal cancer cells. mAb 17-1A has demonstrated activity in the adjuvant setting in surgically treated patients with Dukes stage C colorectal cancer.[66] In comparison with observation alone, post-operative treatment with mAb 17-1A reduced the overall mortality rate by 30% ($p = 0.05$, log-rank) and decreased the recurrence rate by 27% ($p = 0.05$, log-rank) after a median follow-up of 5 years. The antibody markedly suppressed or delayed the emergence of distant metastases, but it did not affect the development of local recurrences. Despite these promising results, mAb 17-1A has not demonstrated significant activity in the treatment of advanced colorectal cancer to date.

Other mAb currently in development include MN-14 and 105AD7 (Table 1). The use of mAb to specifically target a cytotoxic agent to tumor cells has also recently been the focus of considerable research. Examples include Colon DM1 and XomaZyme-791 (Table 1). A further adaptation to this approach is the use of an antibody-vectored enzyme to target a non-cytotoxic prodrug to a tumor site. The ADEPT (ZD2767) technique uses mAb A57 linked to a carboxypeptidase enzyme and a nitrogen mustard prodrug. The mAb targets the tumor and the enzyme facilitates the conversion of the prodrug to an active cytotoxic agent at the tumor site (Table 1).

Other therapeutic approaches

A vast array of other therapeutic approaches are being investigated in the treatment of colorectal cancer and are summarized in Table 2. Examples include the antiangiogenic agent PF 4, which interferes with the formation of new blood vessels and inhibits tumor growth, and the dehydrogenase inhibitor 5-ethinyluracil (776C85), which blocks the degradation of 5-FU.

Gene therapy. Gene therapy is in the very early stages of development but may have a potential role in the treatment of colorectal cancer in the future. One current area of research in this field is the use of an adeno-associated virus vector to carry the cytosine deaminase gene. This gene has been shown to convert the non-toxic prodrug 5-fluorocytosine to 5-FU and its metabolites *in vivo*.[83] A phase I study is planned to investigate the efficacy of this therapy in the treatment of metastatic colorectal cancer.

Potential implications of new anticancer agents

Past efforts to introduce new agents and thus replace the standard chemotherapeutic agent, 5-FU, have proved unsuccessful. However, the 1990s have heralded a new era in drug development for colorectal

Table 1. Examples of monoclonal antibody (mAb) therapies currently in development for the treatment of colorectal cancer (CRC)

Name	Type of product	Mechanism of action	Stage of development	Preclinical/clinical activity	Reference
17-1A	murine mAb: targets CO17-1A tumor-associated antigen expressed on CRC cells	immunostimulant	launched in Germany as postoperative adjuvant therapy in Dukes stage C CRC; phase II (USA); phase I (Japan)	post-operative treatment with 17-1A reduced overall mortality and decreased recurrence rate after a median follow-up of 5 years compared with observation alone in patients with Dukes stage C CRC	66
A7		immunomodulator	clinical (Japan)	mAb A7 conjugated with the anticancer antibiotic neocarzinostatin prolonged survival times when compared with conventional chemotherapy in patients with CRC liver metastases (median survival 328 versus 128 days; $p < 0.05$)	67
MN-14	second-generation CEA-specific murine mAb	immunostimulant	phase II (USA)	MN-14 has been shown to effectively target tumors in cancer patients	68
105AD7	anti-idiotypic mAb	immunostimulant	phase III (USA)	in a phase I/II study of patients with CRC, 105AD7 significantly increased the survival rate; median survival following diagnosis in patients with late-stage disease was 12 versus 3 months in 105AD7 immunized and non-immunized patients, respectively	69
CDP 833	antibody–radioisotope conjugate comprising azamacrocyles conjugated to humanized A33 mAb incorporating the radioisotope yttrium-90 (^{90}Y)	unknown	phase I (USA)	in mice, CDP 833 was associated with complete xenograft tumor regression in the long term; a cross-linked trivalent fragment of humanized mAb A33 linked to ^{90}Y also resulted in complete tumor regressions in xenografted mice	70
Xoma Zyme-791	comprises the mAb Xmmco-791 conjugated to the ricin A chain	immunotoxin	phase I (USA) – orphan drug status	when administered to 17 patients with colon cancer, two of 16 patients with hepatic metastases experienced a decrease in size of large metastases and disappearance of smaller metastases	71
Colon-DM1	immunoconjugate between a humanized anti-colon cancer mAb and cytotoxic maytansinoid compounds	unknown	preclinical (USA)		72

Table 2. Other novel chemotherapeutic agents currently in development for the treatment of colorectal cancer (CRC)

Name	Type of product	Phase of development	Preclinical/clinical activity	Reference
Batimastat	metalloproteinase and collagenase inhibitor	phase II (Europe)	batimastat inhibited human colon tumor growth in a patient-like orthoptic model in nude mice; median survival was 140 and 110 days in the batimastat and control groups, respectively ($p < 0.01$); pivotal phase III studies in the treatment of malignant ascites have been suspended due to the development of inflammation and pain in the abdomen	73
DMP-840	RNA synthesis inhibitor	phase II (USA and Canada)	DMP-840 was used to treat four colon adenocarcinoma xenografts derived from adult patients. Significant growth inhibition was observed in HC_1 and ELC_2 tumors, and a high frequency of partial responses (64–79%) was reported for GC_3 xenografts	74
Droloxifene	estrogen antagonist	phase II (Germany)	estrogen binding receptors have been identified in human colorectal carcinoma cell lines; in a phase II study of patients with CRC pretreated with cytotoxic chemotherapy, six of 15 patients experienced disease stabilization, but no partial or complete responses were reported; in another phase II study, one of nine evaluable patients with metastatic CRC experienced stable disease and eight had disease progression	75, 76
P30 (Onconase)	a ribonuclease microtubule inhibitor	phase II (USA)	demonstrated promising antitumor activity against a number of solid tumors, including non-small cell lung, pancreatic and colorectal tumors	77
776C85 (5-ethynyluracil)	dehydrogenase inhibitor. blocks the catabolism of 5-FU	phase I (UK)	776C85 increased the efficacy and toxicity of 5-FU in mice with Colon 38 and MOPC-315 tumors; the therapeutic index of 5-FU was increased 2- to 4-fold	78
RA 700	protein synthesis inhibitor	phase I (Japan)	RA 700 has demonstrated activity in the treatment of colon 38 cancer cells	
Platelet factor 4 (PF 4)	angiogenesis inhibitor	phase II (USA)	intralesional injections of platelet factor 4 inhibited the growth of primary cutaneous implants of human colon carcinoma cells in mice	79
CI 994	angiogenesis inhibitor	phase I (USA)	–	
Roquinimex	immunomodulator; *in vivo* antitumor activity mediated by enhanced NK cell and non-NK cell activity	phase II (Europe)	–	
OM 163		preclinical (Switzerland)	in a rat colon cancer model OM 163 was effective in reducing tumor size	80
Anti-idiotype CEA antibody vaccine	IgG1 murine monoclonal anti-idiotype antibody designated anti-idiotype CEA antibody vaccine	phase II (USA)	demonstrated specific active immunity to CEA in patients with advanced CRC	81
ZD 2767 (ADEPT)	antibody-directed enzyme prodrug therapy (ADEPT); comprises a conjugate of the $F(ab')_2$ fragment of the anti-CEA antibody A57, carboxypeptidase G2 and a nitromustard analog prodrug	preclinical (UK)	demonstrated approximately 50% tumor regression of LoVo CRC xenografts in athymic mice and tumor growth was delayed for more than 30 days	82
Gastrin 17 vaccine	antihormone immunogen designed to neutralize the hormone gastrin 17	phase II (UK)	in colon cancer animal models, gastrin 17 vaccine markedly reduced tumor growth; there was also a reduction in viable tumor cells, an immune response against the tumor and a reduction in metastatic spread to the lung	

cancer, with intensive research efforts directed at the innovation of novel chemotherapeutic agents with improved efficacy and tolerability profiles compared to standard 5-FU-based regimens. Although many of these agents are currently in the early stages of development, their profusion and varied mechanisms of action provide reason for optimism regarding the management of patients with advanced disease. The three agents anticipated to have the greatest impact on treatment in the near future are ZD1694, irinotecan and oxaliplatin, and it is hoped that the benefits of these and other drugs will ultimately improve the prognosis and further increase the survival of patients with advanced colorectal cancer.

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