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Integrating the oral fluoropyrimidines into the management of advanced colorectal cancer

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Abstract

In colorectal cancer, leucovorin-modulated 5-fluorouracil (5-FU) has been the mainstay of both adjuvant treatment and treatment of metastatic disease for many years. In advanced disease, response rates of 10–43% are reported; efforts to improve efficacy through schedule modification, including prolonged infusions, have led to limited success. New agents with improved efficacy, tolerability and ease of administration are required. Among the newer drugs, irinotecan and oxaliplatin are becoming established as first- and second-line treatment for advanced disease. Their novel mechanisms of action have proven to be of value in 5-FU-resistant patients. In tandem with these developments, thymidylate synthase inhibition has remained an important objective and oral fluoropyrimidines such as capecitabine and UFT (uracil plus tegafur)/leucovorin have been developed with this goal in mind. Two large, phase III studies of capecitabine in metastatic disease demonstrated objective response rates of 26.6 and 24.8%. UFT/leucovorin has also been evaluated in phase III trials, with an 11.7% response rate reported. Both agents are being evaluated in combination with oxaliplatin and irinotecan, and ultimately oral fluoropyrimidines as monotherapy or combination therapy may replace intravenous (i.v.) 5-FU as first-line treatment for metastatic colorectal cancer.

Keywords: Colorectal cancer; 5-Fluorouracil; Fluoropyrimidines; Oral; Capecitabine; UFT; Oxaliplatin; Irinotecan

1. Introduction

Colorectal cancer is one of the most common cancers in Europe and the USA, accounting for 10–15% of all cancers. For patients with localised disease, surgical resection of the tumour is the standard treatment approach, and is usually followed by adjuvant therapy with cytotoxic drugs, with or without radiation. However, 30–40% of these patients will relapse after adjuvant therapy. Furthermore, approximately 20–30% of patients have metastatic disease at the time of presentation, and for these patients treatment is palliative, aiming to control disease progression, induce remission and prolong life while maintaining quality of life.

Until recently, the only agents with proven efficacy were the fluoropyrimidines, such as 5-fluorouracil (5-FU). 5-FU has traditionally been administered as an intravenous (i.v.) bolus at doses in the region of 500 mg/m^2. Objective response rates are typically less than 20% and median survival is approximately 1 year when bolus 5-FU is used as first-line monotherapy for metastatic colorectal cancer [1,2]. There have been numerous attempts to improve response rates through schedule modification and prolonged i.v. infusions, but success has been limited. In response to the need for new agents with improved efficacy, tolerability and ease of administration, new drugs have been developed, including the oral fluoropyrimidine derivatives, which have shown considerable promise.

The increasing emphasis on developing oral agents with at least comparable efficacy but enhanced tolerability, is an important factor when considering the future care of cancer patients. In addition, a questionnaire-based study has confirmed that patients prefer oral to i.v. administration of chemotherapy agents [3]. Oral agents therefore have the potential to provide home-based treatment that may enhance patients' quality of life [4], and may also offer potential economic benefits through reduced nurse and daycare costs [5].

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This article reviews current treatments and presents data on new oral agents, both as monotherapy and as components of combination regimens, in patients with colorectal cancer.

2. Use of leucovorin-modulated 5-FU schedules

The addition of leucovorin to 5-FU schedules results in prolonged inhibition of thymidylate synthase, thus enhancing the principal mechanism of action of 5-FU cytotoxicity. Leucovorin-modulated 5-FU is established in the adjuvant treatment of Dukes' stage C colorectal cancer [6] and in subgroups of patients with Dukes' stage B disease. In addition, most studies of patients with metastatic colorectal cancer have indicated a significantly improved tumour response rate in patients receiving 5-FU plus leucovorin, with response rates of 21–31% for leucovorin-modulated regimens compared with 10–14% for 5-FU alone [1,7,8]. A meta-analysis of nine trials including nearly 1400 patients comparing 5-FU/leucovorin regimens with 5-FU alone confirmed the significantly greater tumour response rates when leucovorin was included in the regimen (23 versus 11%) [9], although improvement in median survival was not observed.

3. Prolonged infusion of 5-FU

It has been estimated that in colon cancer only 3% of cells are in active growth at any one time [10]. 5-FU is active only when cells are in S-phase and the drug has a very short half-life of 8–22 min [11]. In an attempt to prolong cell exposure to 5-FU and improve antitumour activity, the drug has been administered as a prolonged i.v. infusion. However, prolonged i.v. administration has certain limitations because central venous access is required for administration, which is relatively expensive, requires surgery for placement and is associated with significant morbidity. Complications such as infections, bleeding, thrombosis and pneumothorax occur in 15–20% of patients [12]. Prolonged infusion may also have a negative impact on patients' quality of life [13].

Several trials have been conducted to compare the efficacy of 5-FU when administered as an i.v. bolus or as a protracted infusion (continuously for several weeks). A meta-analysis of six trials including 1219 patients found that tumour response rate was significantly higher in patients receiving protracted infusion compared with bolus 5-FU (22 versus 14%, respectively) [14]. Overall survival was also significantly higher with protracted infusion of 5-FU, although median survival rates were similar. Protracted infusion of 5-FU was associated with a lower incidence of haematological toxicity than bolus administration; hand–foot syndrome was more common.

In a more recent, randomised study [15], a twice-monthly schedule of high-dose leucovorin plus bolus 5-FU followed by a 48-h infusion of 5-FU (de Gramont regimen) was found to produce a superior response rate to monthly low-dose leucovorin plus bolus 5-FU (Mayo Clinic regimen) in patients with advanced colorectal cancer (Table 1). Time to disease progression (TTP) was also significantly superior with the infused regimen (median 6.3 versus 5.0 months; $P = 0.001$) (Table 2), although the difference in median survival (14.2 versus 13.0 months) was not statistically significant (Table 3). The bimonthly regimen was less toxic than the monthly regimen. Similarly, a 24-h infusion of 5-FU in combination with weekly leucovorin as a 2-h infusion (German Arbeitsgemeinschaft Internistische Onkologie (AIO) regimen) resulted in significantly superior TTP compared with the Mayo Clinic regimen (median 6.4 versus 4.1 months, respectively) (Table 2), but there was no significant survival benefit [16] (Table 3).

These trials show that although the optimal schedule and dose for 5-FU plus leucovorin combination therapy has not been clearly identified [17], prolonged infusion of 5-FU appears to offer modest benefits in terms of efficacy compared with bolus 5-FU with or without leucovorin, and is also associated with less toxicity.

4. New treatment approaches for colorectal cancer

Although the modifications to dose and schedule described above have resulted in improved response

Table 1
Phase III trials of first-line treatment approaches for metastatic colorectal cancer: response rates

	Response rate (%)			
	Study drug	Mayo Clinic regimen	Relation to Mayo Clinic regimen	*P* value
Capecitabine [33]	25.7	16.7	Superior	< 0.0002
UFT/LV [35]	11.7	14.5	Equivalent	NS
de Gramont regimen[a] [15]	32.6	14.5	Superior	0.0004
AIO regimen [16]	20.5	11.5	Equivalent	NS

NS, non significant; UFT/LV, uracil plus tegafur/leucovorin; AIO, Arbeitsgemeinschaft Internistische Onkologie.
[a] Response rate analysis for the de Gramont regimen included only patients with measurable disease (79% of the intent-to-treat population).

Table 2
Phase III trials of first-line treatment approaches for metastatic colorectal cancer: time to disease progression (TTP)

	Median TTP (months)			
	Study drug	Mayo Clinic regimen	Relation to Mayo Clinic regimen	*P* value
Capecitabine	4.6	4.7	Equivalent	NS
UFT/LV	3.5	3.8	Inferior	0.01
de Gramont regimen[a]	6.3	5.0	Superior	0.0010
AIO regimen	6.4	4.1	Superior	0.02

NS, non significant; UFT/LV, uracil plus tegafur/leucovorin; AIO, Arbeitsgemeinschaft Internistische Onkologie.
[a] TTP analysis for the de Gramont regimen included 98% of the intent-to-treat population.

rates and, in some cases, modest improvements in survival, the prolonged i.v. administration of fluoropyrimidines generally requires indwelling venous access catheters, which are inconvenient, can interfere with patients' lifestyles, and can be associated with medical complications such as infection or thrombosis. The pump systems used for protracted infusion are cumbersome and impact negatively on patients' quality of life. Therefore, there is an unmet medical need for new agents that can be administered orally. In recent years, several enzymes, including thymidylate synthase, dihydropyrimidine dehydrogenase (DPD) and topoisomerase I, have been targeted with the aim of developing an oral agent with an improved safety profile and/or improved antitumour efficacy compared with current treatment options.

5. Raltitrexed

Raltitrexed is a direct thymidylate synthase inhibitor, designed to compete with folinic acid for the binding site of thymidylate synthase. In a phase III trial of 439 chemotherapy-naïve colorectal cancer patients, raltitrexed demonstrated similar efficacy to 5-FU/leucovorin, with objective response rates of 19 and 17%, respectively, and median survivals of 10.1 and 10.2 months, respectively [18]. In a second study comparing raltitrexed with 5-FU plus high-dose leucovorin in 495 patients with advanced colorectal cancer, efficacy was similar in terms of response rates (19% with raltitrexed versus 18% with 5-FU/leucovorin) and median survival (10.9 and 12.3 months, respectively), but TTP was significantly shorter with raltitrexed (median 3.9 versus 5.1 months, respectively, $P < 0.005$) [19].

Another phase III study compared raltitrexed with two other 5-FU-based regimens: the de Gramont regimen and the Lokich regimen (protracted infusion of 5-FU) in 905 patients [20]. Median survival was 10 months in all three groups, but progression-free survival was shorter in the raltitrexed arm than in the other two arms (median 5 months with raltitrexed, 6 months with de Gramont, $P = 0.03$). Of some concern, raltitrexed therapy was associated with more treatment-related deaths than the other two regimens (4% with raltitrexed versus 0% with de Gramont) [21]. Moreover, recently a pan-European trial evaluating raltitrexed in the adjuvant setting was prematurely closed because of excess deaths in the raltitrexed arm. Raltitrexed is excreted by the kidney and it is now recommended that patients should have a measured (or calculated) creatinine clearance > 1.1 ml/s to be suitable for treatment.

6. Oral fluoropyrimidines

Another approach to achieving prolonged inhibition of thymidylate synthase is the oral administration of fluoropyrimidines. The unpredictable and highly variable bioavailability of 5-FU make it unsuitable for oral administration, but a number of new oral fluoropyrimidines have been developed to overcome these

Table 3
Phase III trials of first-line treatment approaches for metastatic colorectal cancer: overall survival

	Median survival (months)			
	Study drug	Mayo Clinic regimen	Relation to Mayo Clinic regimen	Hazard ratio[b] (95% CI)
Capecitabine	12.9	12.8	Equivalent	0.96 (0.85–1.08)
UFT/LV	12.4	13.4	Equivalent	1.08 (0.92–1.27)
de Gramont regimen[a]	14.2	13.0	Equivalent	NA
AIO regimen	13.2	12.0	Equivalent	NA

NS, non significant; UFT/LV, uracil plus tegafur/leucovorin; AIO, Arbeitsgemeinschaft Internistische Onkologie; NA, not available.
[a] Survival analysis for the de Gramont regimen included 98% of the intent-to-treat population.
[b] Hazard ratio > 1 represents improved survival in the Mayo Clinic regimen arm.

problems. There are essentially two approaches that have been explored: tumour-selective activation of a 5-FU precursor by an enzyme localised in tumour tissue, and combination of an oral fluoropyrimidine (such as tegafur or oral 5-FU) with a DPD inhibitor in order to reduce the rate of 5-FU metabolism.

6.1. Capecitabine

The first approach was used in the design of capecitabine, a fluoropyrimidine carbamate. Capecitabine has no antitumour activity itself but is metabolised in the body via three sequential enzyme steps to produce 5-FU within tumours (Fig. 1). Following rapid absorption, capecitabine passes unchanged into the liver for the first step in its activation [22]. It is then converted to a second intermediate by cytidine deaminase. The enzyme thymidine phosphorylase catalyses the final conversion to 5-FU and is present at significantly higher concentrations in tumour tissue compared with adjacent normal tissue in a range of solid tumour types, including breast and colorectal cancers, resulting in tumour-selective generation of 5-FU [23]. The tumour selectivity of capecitabine has been demonstrated in preclinical models [24] and in a phase II study in patients with colorectal cancer [25]. Studies in human cancer xenograft models have also indicated that the efficacy of capecitabine correlates with the ratio of thymidine phosphorylase to DPD in tumours [26]. Furthermore, treatments that can increase thymidine phosphorylase activity in the tumour, such as taxoids, mitomycin C, cyclophosphamide and radiotherapy, may be synergistic with capecitabine [27–29].

Based on the encouraging results of a randomised, phase II, dose-selection trial in 109 patients with colorectal cancer [30], two large, randomised, phase III trials were undertaken in colorectal cancer patients who were previously untreated for advanced and/or metastatic disease [31,32]. The trials compared an intermittent schedule of oral capecitabine (1250 mg/m^2 twice daily for 14 days followed by 7 days' rest) with the Mayo Clinic regimen of bolus 5-FU/leucovorin, days 1–5 every 4 weeks. Each trial included more than 600 patients.

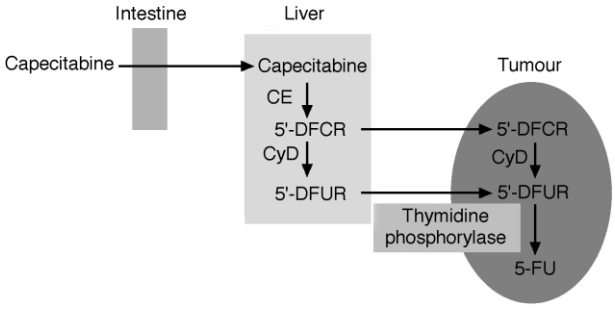

Fig. 1. Enzymatic conversion of capecitabine to 5-FU. CE, carboxylesterase; CyD, cytidine deaminase.

The trials demonstrated that capecitabine achieved response rates superior to 5-FU/leucovorin when administered as first-line therapy to patients with metastatic colorectal cancer. In the trial conducted in Europe, Taiwan, Israel and Australasia the response rate was significantly superior with capecitabine (26.6 versus 17.9% with 5-FU/leucovorin; $P = 0.013$), with an equivalent median TTP of 5.2 versus 4.7 months with 5-FU/leucovorin [31]. Similar results were seen in the study conducted in the USA, Mexico and Brazil: the response rate with capecitabine was 24.8% compared with 15.5% ($P = 0.005$) in the Mayo Clinic regimen group [32]. A recently presented, prospectively planned analysis of the pooled data from these two studies confirmed the superior response rate and equivalent TTP achieved with capecitabine (Tables 1 and 2) [33]. In addition, survival in patients receiving capecitabine was equivalent to that achieved with the Mayo Clinic regimen (median 12.9 versus 12.8 months with Mayo Clinic regimen, hazard ratio = 0.96, $P = 0.48$) (Table 3) [33].

The safety profile exhibited in these trials generally favoured capecitabine compared with the Mayo Clinic regimen. There was significantly less diarrhoea, stomatitis, nausea and alopecia (all grades) in patients treated with capecitabine compared with the Mayo Clinic regimen. The incidence of grade 3/4 stomatitis and neutropenia was significantly lower and alopecia was rare in patients receiving capecitabine. However, the hand–foot syndrome, a cutaneous syndrome affecting the palms and soles, was relatively common in patients receiving capecitabine in both studies, but was manageable with treatment interruption and dose reduction if necessary. This adverse event is known to be associated with prolonged 5-FU exposure, as exemplified by the protracted infusion schedules.

6.2. UFT/leucovorin

A second oral fluoropyrimidine regimen, UFT/leucovorin has also been investigated extensively in phase III trials. UFT is a combination of tegafur (an oral precursor of 5-FU) and uracil (a reversible DPD inhibitor) in a 1:4 molar ratio. The uracil component of UFT is included to prolong 5-FU activity by preventing its rapid breakdown. A phase II trial evaluating UFT 300–350 mg/m^2/day in combination with leucovorin 150 mg/m^2/day for 4 weeks, followed by a 1-week rest period, demonstrated an objective response rate of 42% [34]. 5 of 7 patients treated with 350 mg/m^2/day UFT developed prolonged grade 3 diarrhoea, and therefore the dose was reduced to 300 mg/m^2/day for all remaining patients. At this dose, only 4 of 38 patients developed grade 3 diarrhoea, and therefore a dose of 300 mg/m^2/day was selected for phase III evaluation.

Two large, randomised, phase III trials have been conducted to compare UFT/leucovorin with a bolus

regimen of 5-FU/leucovorin. In the first of these trials, which was conducted in several centres in the USA, Canada and Europe, bolus 5-FU/leucovorin was administered in a 4-weekly cycle (Mayo Clinic regimen). Response rates in the two treatment groups were equivalent (11.7 versus 14.5%, respectively), as was median survival (12.4 versus 13.4 months, respectively) (Tables 1 and 3) [35]. However, TTP was inferior with UFT/leucovorin (3.5 versus 3.8 months with Mayo Clinic regimen, $P = 0.01$) (Table 2). UFT/leucovorin was associated with a lower incidence of leucopenia and thrombocytopenia than the Mayo Clinic regimen, and a lower incidence of infection (all grades: 22 versus 30%, respectively, $P < 0.05$; grade 3–4: 2 versus 7%, respectively, $P < 0.05$). There was a trend towards a higher incidence of grade 3/4 diarrhoea in the UFT/leucovorin group (21 versus 16%), but stomatitis and mucositis were significantly less common with the oral regimen (24 versus 75%, respectively, $P < 0.001$). Hyperbilirubinaemia was significantly more common with UFT/leucovorin than with the Mayo Clinic regimen (all grades: 39 versus 22%, $P < 0.001$; grade 3–4: 15 versus 8%, $P < 0.05$).

The second, confirmatory study, conducted in Europe, Canada, Australia and New Zealand, included 380 patients with metastatic colorectal cancer [36]. However, it should be emphasised that in this study, the control arm was a modified Mayo Clinic regimen, with bolus 5-FU/leucovorin administered on days 1–5 every 5 weeks rather than every 4 weeks. The median survival, median TTP and response rates were statistically equivalent in the two treatment arms, and the safety profile was similar to that observed in the phase III trial described above. Differences in grade 3/4 infection, diarrhoea and hyperbilirubinaemia were not statistically significant.

6.3. Other fluoropyrimidines

New agents in earlier stages of clinical development include eniluracil and 5-chloro-2,4-dihydroxypyridine (CDHP). These agents were designed as potent inhibitors of DPD that potentially enable oral administration of 5-FU and improve its therapeutic index [5]. In a phase II study of 75 colorectal cancer patients treated with eniluracil plus oral 5-FU (with or without leucovorin), a 21% response rate was observed in the subpopulation of patients with previously untreated disease [37]. Myelosuppression was frequent and dose-limiting, and neutropenic sepsis was reported in 14% of patients. Further clinical development of the 5-FU/eniluracil combination has been abandoned.

Another potential combination of an oral fluoropyrimidine and a biomodulator is S-1, a fixed combination of tegafur, CDHP and oxonic acid. Oxonic acid inhibits phosphoribosyl transferase and may be able to protect against diarrhoea caused by the release of 5-FU directly into the gastrointestinal tract. In rats bearing advanced colorectal carcinoma xenografts, S-1 had greater antitumour activity and a better therapeutic index than oral tegafur or continuous infusion 5-FU [38]. A phase I trial in patients with advanced solid tumours identified a regimen of 40 mg/m^2 twice daily, days 1–28 every 5 weeks, in patients previously exposed to minimal or no chemotherapy, and 35 mg/m^2 in heavily pretreated patients [39]. Diarrhoea was the dose-limiting toxicity. A recently reported phase II trial of S-1 40 mg/m^2 twice daily as first-line therapy for metastatic colorectal cancer showed a response rate of 35% in 62 eligible patients, with a median survival of 12 months [40]. Grade 3/4 neutropenia was reported in 13% of patients, and gastrointestinal events were the other principal toxicity.

7. Can oral fluoropyrimidines replace intravenous 5-FU?

Oral agents offering at least equivalent efficacy with improved safety profiles provide important alternatives to intravenous 5-FU. Oral administration carries the obvious advantage of convenience for patients, and is likely to be associated with pharmacoeconomic benefits. The data on the efficacy and safety of oral fluoropyrimidines suggest that these agents may well replace i.v. 5-FU as the optimal method of administering a fluoropyrimidine. In addition, the favourable safety profile of these agents makes them a suitable option for the treatment of patients for whom the administration of i.v. chemotherapeutic agents may be difficult, such as the elderly. It is unlikely that the oral fluoropyrimidines will be effective in the treatment of patients exposed to prior 5-FU-based regimens, but further clinical studies are required in the second-line setting. Continuous infusion schedules of 5-FU have activity in patients who are resistant to bolus therapy, and administration of doxifluridine, a precursor of 5-FU, resulted in a 13% objective response rate in patients who had relapsed after 5-FU therapy [41]. Preclinical studies have shown that capecitabine produces higher tumour 5-FU concentrations than can be achieved with maximally tolerated doses of 5-FU itself [24], and therefore this agent could be of value in 5-FU-resistant disease. In contrast, two studies of UFT/leucovorin failed to show any response in a subgroup of patients with 5-FU-refractory colorectal cancer, and in a phase II trial the combination of eniluracil/5-FU showed little efficacy in patients with 5-FU/leucovorin-refractory metastatic disease [37].

8. Irinotecan

Irinotecan is a semi-synthetic derivative of camptothecin that targets topoisomerase I, the enzyme that catalyses the cleavage and resealing of supercoiled DNA and is essential for DNA replication and transcription.

Following demonstration of the activity of irinotecan *in vitro*, phase I studies were conducted to investigate a range of schedules. In phase II trials, irinotecan demonstrated antitumour activity in both chemotherapy-naïve patients and patients who showed disease progression with 5-FU therapy.

In randomised trials in patients with 5-FU-resistant disease, irinotecan has been shown to significantly prolong survival compared with best supportive care or 5-FU given by infusion [42,43] More recently, further clinical trials have been conducted to investigate the efficacy and safety of irinotecan in combination with 5-FU/leucovorin as first-line therapy. A phase III, multicentre study compared weekly or twice-weekly 5-FU/leucovorin with the same regimen plus irinotecan in 385 patients [44]. The addition of irinotecan to the 5-FU/leucovorin regimen was shown to significantly improve the response rate (41 versus 31%; $P < 0.001$ for evaluable patients; 35 versus 22%; $P < 0.005$ for intent-to-treat population) and TTP (median 6.7 versus 4.4 months; $P < 0.001$). Survival was also significantly superior in the irinotecan group (median 17.4 versus 14.1 months; $P = 0.031$). Grade 3/4 diarrhoea occurred in 44% of patients receiving the irinotecan regimen compared with 26% in patients not receiving irinotecan, and grade 3/4 neutropenia occurred in 29% with irinotecan compared with 2% without irinotecan.

Another phase III trial in first-line treatment, which compared the Roswell Park regimen (leucovorin 20 mg/m^2 plus 5-FU 500 mg/m^2, both administered intravenously on days 1, 8, 15 and 22 every 6 weeks) plus irinotecan versus the Mayo Clinic regimen versus irinotecan alone, demonstrated a significantly superior response rate in the triple combination group (50 versus 28 versus 29%, respectively; $P < 0.001$ for the triple combination versus the Mayo Clinic regimen) and significantly improved progression-free survival (median 7.0 versus 4.3 versus 4.2 months, respectively; $P = 0.004$ for the triple combination versus the Mayo Clinic regimen) [45]. Most importantly, median overall survival was significantly improved with the triple combination (14.8 versus 12.6 months with the Mayo Clinic regimen; $P = 0.04$; 12.0 months with irinotecan alone). The results of this study were analysed in combination with the two-arm phase III study described above [46]. The analysis showed that the combination of irinotecan with 5-FU/leucovorin as first-line therapy significantly improved tumour control compared with 5-FU/leucovorin alone, giving a significant improvement in overall survival ($P = 0.009$).

9. Oxaliplatin

Oxaliplatin is a platinum compound that has demonstrated activity in preclinical studies of colorectal carcinoma cell line xenografts, as well as cisplatin-resistant cell lines [47]. In phase II trials of patients with advanced colorectal cancer resistant to 5-FU, oxaliplatin resulted in an objective response rate of 10–11% [48]. The dose-limiting toxicity was peripheral sensory neuropathy, occurring in 18–31% of patients. Nausea, vomiting and diarrhoea have also been reported.

Several studies have investigated the combination of leucovorin, 5-FU and oxaliplatin and results have suggested synergism for the combination. In two studies exploring an oxaliplatin dose of 100 mg/m^2, response rates were 46 and 27% [49,50]. Further evaluation of the combination indicated that the dose of oxaliplatin may be important since a subsequent study using a lower dose of oxaliplatin (85 mg/m^2) resulted in an objective response rate of only 21–22% [51]. Furthermore, a small study investigating oxaliplatin at a dose of 130 mg/m^2 in combination with 5-FU/leucovorin demonstrated a response rate of 44%, with a response rate of 52% in patients refractory to 5-FU/leucovorin [52]. However, these high response rates have not been reproduced in large, multicentre studies.

Evaluation of oxaliplatin as first-line therapy has also been undertaken, and two large, randomised, phase III trials have been reported. Results of these trials have shown that first-line treatment comprising intensified chemotherapy plus oxaliplatin improves response rates and TTP in patients with advanced colorectal cancer, but no significant improvements in survival time were observed in either trial [53,54]. However, the apparent lack of effect of oxaliplatin on survival in one of the studies may be explained by the crossover design of the trial [53], because patients failing treatment with 5-FU/leucovorin were crossed over to oxaliplatin or other therapy.

10. Combination regimens

There is still room for significant improvement in the management of advanced colorectal cancer. The efficacy of infused 5-FU can be improved with the addition of agents such as irinotecan or oxaliplatin, and efficacy and tolerability may be further improved by replacing 5-FU with an orally active fluoropyrimidine. The evaluation of agents such as capecitabine and UFT/leucovorin in combination with irinotecan and oxaliplatin is an important priority. Phase I and II trials are in progress to assess the feasibility of these combination regimens, and preliminary data are encouraging.

A phase I dose-escalation study investigating the combination of capecitabine plus irinotecan showed that the combination is feasible with clinical activity. Data from an extension of the study were recently presented and indicate that the preliminary recommended dose is capecitabine 1000 mg/m^2 twice daily, days 1–14

and 22–35, in combination with weekly irinotecan 70 mg/m^2, weeks 1–6, repeated at day 50 [55]. Additional patients have been enrolled to further validate the tolerability of the recommended dose level and therapy is ongoing in these patients. A phase I, dose-finding study has also been undertaken to investigate capecitabine in combination with oxaliplatin. The study included 23 patients with pretreated advanced/metastatic solid tumours [56]. The principal dose-limiting toxicity was diarrhoea, which occurred in 1 of 9 patients treated at the capecitabine 1000 mg/m^2 dose level and 2 of 8 patients treated at the 1250 mg/m^2 dose level. Therefore, a regimen of oral capecitabine 1000 mg/m^2 twice daily (days 1–14) combined with i.v. oxaliplatin 130 mg/m^2 (day 1) every 21 days was identified as the recommended dose for further development. The combination also demonstrated promising antitumour activity in the 9 patients with metastatic colorectal cancer, all of whom had been pretreated with 5-FU-based regimens and 5 of whom had received prior irinotecan. Partial responses were observed in 5 patients (of whom 4 had received prior irinotecan), with a further 3 patients achieving disease stabilisation.

UFT/leucovorin has also been investigated in combination with both irinotecan and oxaliplatin, and recently presented data suggest that both of these combinations are feasible. In a phase I/II trial of irinotecan plus UFT/leucovorin as first-line therapy in 33 patients with advanced or metastatic colorectal cancer, the dose-limiting toxicities included diarrhoea and febrile neutropenia [57]. The dose identified for further evaluation was UFT 250 mg/m^2/day plus leucovorin 90 mg/day (both administered as three divided doses, days 1–14) in combination with irinotecan 250 mg/m^2 on day 1 every 3 weeks. Preliminary efficacy results were promising, and a phase II extension of the study is being conducted.

In a phase I/II trial evaluating the combination of UFT/leucovorin plus oxaliplatin [58], the incidence of grade 3/4 toxicities was relatively high in the first 16 patients, and therefore the dose of UFT was reduced from 390 to 300 mg/m^2/day, days 1–14. At the lower dose, grade 3/4 diarrhoea occurred in 21% of 50 patients, and therefore this is the recommended dose for oxaliplatin/UFT/leucovorin combination therapy.

11. Conclusions

The treatment options for patients with advanced colorectal cancer are expanding rapidly. Irinotecan is considered by many to be the gold standard for the second-line treatment of metastatic colorectal cancer following disease progression on a 5-FU-based regimen. In the first-line setting, irinotecan administered in combination with 5-FU/leucovorin significantly improves survival and progression-free survival. Oxaliplatin also appears to improve response rates and progression-free survival when used in combination with 5-FU/leucovorin, although a statistically significant survival benefit has not yet been demonstrated in the phase III setting.

Another interesting class of agents, the oral fluoropyrimidines, is likely to become important in the first-line therapy of metastatic colorectal cancer. A recent, randomised study demonstrated a strong preference among patients for oral versus i.v. therapy [59]. The oral fluoropyrimidines offer benefits in terms of convenience, and capecitabine monotherapy has demonstrated a response rate significantly superior to that achieved with the Mayo Clinic regimen. Extensive phase III clinical evaluation also suggests that both capecitabine and UFT/leucovorin offer safety benefits.

In addition to their potential role as monotherapy, the oral fluoropyrimidines are interesting combination partners for drugs with different mechanisms of action but which are potentially myelosuppressive, such as irinotecan and oxaliplatin. The increasing emphasis on developing oral agents with at least equivalent efficacy, but enhanced tolerability, is an important component of the future care of cancer patients. Oral agents offer the advantage of home-based chemotherapy and potential cost benefits for healthcare providers. It is possible that as development of these agents continues, the most effective oral fluoropyrimidines may replace standard 5-FU as first-line chemotherapy for metastatic colorectal cancer, either as monotherapy or in combination with agents such as irinotecan or oxaliplatin.

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