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Development of Treatment for Advanced Colorectal Cancer: Infusional 5-FU and the Role of New Agents

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Despite the fact that it was first introduced as a cancer treatment over 30 years ago, the mainstay cytotoxic agent for the treatment of metastatic colonic cancer is still 5-fluorouracil (5-FU). However, even after all this time, there is still no standard schedule for 5-FU administration which is recognised by the oncology profession. Bolus infusion remains the most popular choice, but recent investigations into short- and long-term continuous infusion schedules of 5-FU have offered advantages in terms of objective response rates and toxicity. In addition, combination infusion regimens (whereby the effectiveness of 5-FU is modulated through its co-administration with other agents or chronomodulation) are becoming accepted, although, once again, there is no recognised standard treatment regimen. This paper reviews the data from those non-comparative studies in which 5-FU has been administered as monotherapy, and relates this to data from studies of 5-FU co-administration with folinic acid and interferon. Data from other treatment regimens, which include topoisomerase I inhibitor schedules and chronomodulation of 5-FU with oxaliplatin, are presented. The advantages and disadvantages of these different regimens based upon these non-comparative data, and their position relative to standard therapies, are discussed. The likely developments with regard to the clinical and health-economic requirements for newer treatment are outlined. Copyright © 1996 Elsevier Science Ltd

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INTRODUCTION

COLORECTAL CANCER is the second largest cause of death from cancer [1], with the world-wide prevalence from the disease exceeding 3.5 million [2].

The most active single cytotoxic agent against metastatic colorectal cancer is still 5-fluorouracil (5-FU), despite this agent having been introduced over 30 years ago [3]. Although response rates with 5-FU are far from ideal (usually less than 20%), recent innovations in the use of this agent have increased its efficacy and, in some instances, have increased patient survival [3]. These new treatment regimens are also used to treat those patients who do not respond to 5-FU alone by combining 5-FU with other anticancer agents.

The combination of 5-FU and leucovorin (LV) has become the standard treatment, but there is no agreed standard administration schedule [4]. Commonly used regimens include: 5-FU (425 mg/m^2) plus LV (20 mg/m^2), both given by rapid intravenous (i.v.) injection, daily for 5 days [5] every 4 or 5 weeks and 5-FU (500 mg/m^2) plus LV (500 mg/m^2), both given by rapid i.v. injection weekly for 6 weeks, followed by 2 weeks' rest and then repeated [6]. However, the 5-day 'monthly' regimen (i.e. the Mayo Clinic protocol) tends to be the most appropriate because it is associated with less severe toxicity and it is also the least expensive. In addition, patients find this regimen most acceptable, as they receive treatment only once a month, followed by an interval of 4 weeks, in contrast to the alternative of a single day's treatment every week.

Finally, alternative agents are currently being investigated in clinical trials. These include: the direct and specific thymidylate synthase inhibitor 'Tomudex'^{TM}* (raltitrexed formerly known as ZD1694); the topoisomerase inhibitors, such as irinotecan and topotecan; and the platinum analogues, such as oxaliplatin. Clinical evidence is needed to show which of these agents show promise either as a monotherapy or as combination therapy with 5-FU.

The aim of this article is to review the data from those non-comparative studies which have investigated the effectiveness of these different treatment regimens and treatment schedules.

ESTABLISHED TREATMENTS

The use of systemic 5-FU-based chemotherapy has been shown to improve the median survival of patients with advanced colorectal cancer. Different regimens have been used in an attempt to increase the efficacy of 5-FU through modification of the dosing regimen. Because colon cancer is a slow-growing cancer, with fewer than 3% of the tumour cells actively dividing at any one time [3], a promising approach to treatment

* 'Tomudex' is a trademark, the property of Zeneca Limited.

Table 1. Dosages of 5-FU achieved through different schedules [8]

5-FU schedule	LV	Route	mg/m²	Total dose mg/m²/month
Daily × 5	−	bolus	400	2000
Weekly	−	bolus	750	3000
Daily × 5	−	CI	1000	5000
Daily × 28	−	CI	300	8400
24-h weekly	−	CI	2600	10400
	+	CI	2600	10400
48-h weekly	−	CI	3000	12000

CI, continuous infusion. LV, leucovorin. Reprinted by permission from Diaz-Rubio E, *et al.*, *J Infusional Chemother* 1994, Vol. 4, pp. 58–61.

is to use a continuous infusion of high-dose 5-FU. *In vitro* work suggests that enhanced tumour cell kill occurs in systems which increase the duration of 5-FU exposure [7], with such a regimen having several theoretical advantages over the traditional method of 5-FU bolus infusion [3], including less resistance to 5-FU treatment, improved toxicity and achievement of higher dosages of 5-FU.

For example, a continuous daily infusion of 5-FU (1000 mg/m²) for 5 days allows a total dose of 5000 mg/m²/month to be achieved, compared with the 2000 mg/m²/month achieved with an identical bolus of 5-FU (400 mg/m²) (Table 1). Altering the period over which the 5-FU infusion takes place can also drastically alter the total dose of 5-FU reached; for example a 24-h continuous infusion of 2600 mg/m² 5-FU once a week gives a total dose of 10 400 mg/m²/month, whilst a 48-h infusion of 3000 mg/m² 5-FU weekly gives a total dose of 12 000 mg/m²/month, several times higher than the doses achieved by bolus 5-FU schedules. However, at present, there is little clinical evidence to indicate that the continuous infusion of 5-FU provides a higher concentration of the active metabolite 5-fluoro-deoxyuridine monophosphate for the dividing tumour cells. Due to the different capacity of the cells to catabolise or anabolise 5-FU, a higher 5-FU dose does not necessarily mean more active 5-FU anabolites. However, it has been demonstrated by extensive *in vitro* work [9] that the mechanism of resistance developing after a bolus or continuous infusion of 5-FU application is different; e.g., in cell lines which are resistant to bolus 5-FU, a prolonged exposure still achieves significant cell kill whereas the application of bolus 5-FU after prolonged exposure of the cells to 5-FU does not result in enhanced cell kill. This different behaviour is associated with different mechanisms of resistance to 5-FU, e.g. increase of thymidylate synthase and decrease of RNA in co-operation with FU metabolites [9]. The possible superiority of high-dose infusional 5-FU may be a consequence of a higher dose in conjunction with a different mechanism of resistance (and action) under infusional 5-FU in comparison with bolus 5-FU (A Harstrick, personal communication).

Table 2 outlines the trials comparing protracted continuous infusion with bolus infusion scheduling of 5-FU, and shows that some of these regimens offer significant advantages in terms of objective response rates. The Mid-Atlantic Oncology Program (MAOP) study [10], for example, showed a significant difference in objective response (OR) rates between 5-FU continuous infusion and bolus infusion schedules (30% versus 7%, respectively, $P = 0.001$), whilst the French study [13] showed a slightly smaller (albeit still significant) difference in OR rates (19% versus 8%, respectively, $P = 0.02$). However, in neither of these studies was this significant improvement in OR rate translated into a better survival rate. A logical step on from 5-FU continuous infusion monotherapy is to use such a 5-FU infusion regimen in combination with other drugs which modulate the effect of 5-FU, for example LV [14, 15] or interferon [16]. De Gramont [17] has shown a significantly higher remission rate with a combined treatment of bolus LV plus a bi-weekly 48-h infusion of 5-FU when compared to the 5-FU/LV bolus (5 days) standard protocol. However, the improvement in the survival rate was only borderline.

These promising data need to be confirmed in a randomised prospective study. The continuous infusion treatment regimen being used in the current multicentre trial of the Gastrointestinal Tumour Study Group of the European Organization for the Research and Treatment of Cancer (EORTC) should go some way towards providing such information. This is an important study comparing weekly high-dose infusional 5-FU ± LV with the standard Mayo Clinic protocol (i.e. 5-FU 2600 mg/m², 24-h continuous infusion every week for 6 weeks, repeated every 9 weeks; FU 2600 mg/m², 24-h continuous infusion, weekly for 6 weeks, repeated every 9 weeks plus LV 500 mg/m², 2-h infusion; 5-FU 425 mg/m², bolus infusion for 5 days, repeated every 4–5 weeks plus LV 20 mg/m², bolus infusion) and should be supported by as many European centres as possible. Further studies are investigating the possible advantages of weekly or bi-weekly, high-dose, infusional 5-FU plus LV [17].

Table 2. 5-FU continuous infusion regimens—response rates and survival rates compared with bolus schedules

Group	No. patients	5-FU bolus (mg/m²)	5-FU continuous infusion (mg/m²)	Response rate (%) Bolus	Response rate (%) Infusion	Survival (%) Bolus	Survival (%) Infusion
MAOP [10]	174	500 d 1–5 q 5 w	300 × 70 d	7	30 ($P = 0.001$)	10.3	11.2
NCI-C [11]	184	450 d 1–5 q 4 w	350 × 14 d	6	12 ($P = 0.34$)	9.5	9.5
ECOG [12]	450	500 d 1–7 then weekly	300 daily	19	27 ($P = 0.12$)	10.6	13.0
French [13]	155	500 d 1–5 q 4 w	750 d 1–7 q 3 w	8	19 ($P = 0.02$)	9.0	10.0

q w, repeated every *x* weeks; d, days; MAOP, Mid-Atlantic Oncology Program; NCI-C, National Cancer Institute of Canada; ECOG, Eastern Co-operative Oncology Group.

Table 3. Topoisomerase I inhibitors—CPT-11 schedules examined [21]

Dose	Frequency	Country	Objective response (%)	Complete response (%)
100–150 mg/m^2	2 weekly	Japan	27	0
350 mg/m^2	3 weekly	France	18	?
125 mg/m^2	weekly × 4–6	U.S.A.	24	2
125–150 mg/m^2	weekly × 4–6	U.S.A.	25	2

The disadvantage of 5-FU continuous infusion regimens, such as those described above, is that they require much effort by medical, nursing and pharmacy personnel. Such drugs must be formulated correctly, delivered according to complex regimens and require costly equipment to administer and monitor their infusion correctly. Such regimens, therefore, have an inherently health-economic cost in terms of time and effort of oncology carers, with an additional negative impact on patient quality of life. Although the toxicity of infusional 5-FU is less in comparison to the bolus schedules, these objective disadvantages can only be justified if, in this palliative treatment situation, besides an improvement in the quality of life, a significant and relevant prolongation of life expectancy is achieved.

NEW AGENTS

The heterocyclic alkaloid, camptothecin, together with those of its analogues which have reached advanced clinical development (irinotecan and topotecan), are the only inhibitors of topoisomerase I, thus far, with proven antitumour activity [18]. DNA topoisomerase I is the unique target for camptothecins; during DNA replication, topoisomerase I transiently breaks a single strand of the DNA double helix, thereby reducing torsional strain at the replication point and unwinding DNA ahead of the replication fork [19]. In eukaryotic cells this enzyme has important roles in chromatin organisation, in mitosis and in DNA replication, recombination and transcription. It is postulated that the cytotoxicity of the camptothecins, which are highly S phase-specific agents, lies in their ability to arrest replication by converting the normal replication procedures of transient breakage/cleavage/re-ligation of the DNA strand into permanent DNA breaks [20].

Several phase II studies of CPT-11 have investigated different dosage regimens in advanced colorectal cancer (Table 3). Depending upon the regimen used, OR rates have varied from 18% to 27%, which is not markedly different from those obtained with 5-FU-based regimens. However, in patients progressing under adjuvant or palliative 5-FU-based chemotherapy, CPT-11 yields an OR rate of 16%. CPT-11 is, therefore, at present the only single agent available which has significant antitumour activity in 5-FU resistant disease [22].

The limitation for the use of CPT-11, indeed to the topoisomerase I inhibitors as a group, would seem to be their side-effect profile. There is a high degree of variation in toxicity with topotecan, the maximum tolerated dose being highly schedule-dependent [18]. Patients seem able to tolerate less total drug when it is given in regimens which use continuous infusion or daily bolus infusions than when it is given by intermittent injections. This is reflected in clinical trials where myelosuppression (predominantly neutropenia) is dose-limiting [18].

In contrast, the maximum tolerated dose of a continuous infusion of CPT-11 is similar to that of bolus administration [23], but CPT-11 pharmacokinetics are complex, as its major metabolite (SN-38) is more potent than the parent compound [24]. Thus, in clinical trials, the dose-limiting toxicities of CPT-11 are leucopenia and diarrhoea, with bolus/short-duration schedules seeming to produce more leucopenia than diarrhoea, whilst diarrhoea is the more common using 5-day continuous infusion schedules [23, 25]. Although these side-effects are manageable (for example, early-onset diarrhoea, which occurs during or shortly after infusion, can be controlled with anticholinergic drugs, whilst late-onset diarrhoea can be prevented by loperamide), the high incidence of Grade 3 or 4 toxicity with CPT-11 does cause concern.

Because of this level of toxicity, the use of topoisomerase I inhibitors would seem to be limited to those centres experienced in managing both the treatment therapy and the side-effects produced by the treatment. In addition, although response rates with these agents look promising, their role would seem to be limited to that of second-line therapy for those patients resistant or refractory to 5-FU/LV treatment. For example, it has been shown that in patients who had been pretreated with bolus 5-FU/LV, the overall response rate was 18% compared with an overall response rate of 21% in those chemonaive patients [26].

CHRONOMODULATION AND OXALIPLATIN

There is now much evidence suggesting that the therapeutic index of a particular therapy can be improved, whilst at the same time its toxicity can be minimised, purely by the time of day at which it is administered [27]. For example, the toxicity of at least 20 chemotherapeutic agents depends upon the time of day in murine systems, and their anticancer effects, given either singly or in combination, depend upon circadian factors [18]. Oxaliplatin, a platinum analogue, is one of the family group of *cis*-diamminedichloroplatinum (CDDP) compounds which also includes cisplatin; this agent has little bone marrow toxicity, but dose-limiting pathology is expressed via neurotoxicity.

Oxaliplatin is of specific interest here, as preclinical and clinical studies indicate that oxaliplatin effectively modulates 5-FU above a meaningful single-agent activity of 10% in 5-FU pretreated patients [28].

Table 4 presents the data from recent work by De Gramont [29]. In patients who had been pretreated with 5-FU/LV, there was a 46% overall response rate. However, in those patients who were refractory to 5-FU/LV treatment, combination treatment with oxaliplatin using the same 5-FU/LV infusion schedule also gave an OR rate of 43%.

In another trial [30] in untreated patients, 5-FU (600 mg/m^2 per day) plus LV (300 mg/m^2 per day) and oxaliplatin (25 mg/m^2 per day) were administered as a 5-day continuous infusion, every 3 weeks either at a flat rate or by circadian rhythmic delivery (peak flow rates at 4 h for 5-FU and LV and 16 h for oxaliplatin). Chronomodulation of 5-FU/LV by oxaliplatin increased the OR rate to 50% from 30% (Table 4). These

Table 4. Efficacy and side-effects of oxaliplatin and 5-FU/LV combinations

	De Gramont [29]		Levi [30] Untreated	
	Pretreated	Refractory	Flat	Chrono-modulated q 3 w
Patient number	46	22	93	91
Objective response	46%	43%	30%	50%
Remission duration	8 months +			
Survival	12 months +			
Stomatitis	68%		75%	15%
Neuropathy >2	100%		29%	15%

q w, repeated every *x* weeks. LV, leucovorin.

response rates were further improved when the 3-week treatment cycle was reduced to 2 weeks (OR 69%). If confirmed by prospective trials, this order of response is more usually associated with breast cancer. In addition, the chronomodulated treatment regimens gave a much lower incidence of stomatitis and neuropathy.

CONCLUSION

At present, the standard, first-line therapy for metastatic colorectal cancer is 5-FU, delivered by bolus infusion for 5 days, according to the Mayo Clinic protocol. However, different delivery regimens, with short or prolonged infusion of 5-FU alone and in combination with LV, show much promise. Further work is needed to define the most appropriate 5-FU mono-combination treatment schedules with regard to response rates, survival rates, quality of life and costs and also to define whether such regimens are appropriate as first- or second-line treatments. A current EORTC study of the Gastrointestinal Tract Tumour Study Group is investigating a weekly, high-dose infusion of 5-FU ± LV in comparison with the standard 5-FU/LV bolus schedule according to the Mayo Clinic protocol. Several further studies in France and Spain are also investigating similar protocols.

Because of the toxicity associated with its use, and its demonstrated efficacy in 5-FU refractory patients, CPT-11 should be viewed as a second-line therapy. Chronomodulation of 5-FU/LV in combination with oxaliplatin looks very promising, especially in 2-weekly treatment cycles, but these data need to be treated with caution until confirmed by properly controlled, randomised, prospective studies. Based on the data discussed above, new agents, such as 'Tomudex', will fulfil their promise as first-line treatment if they can either improve, or match, the response rates of 5-FU regimens, and also improve upon 5-FU in terms of side-effect profile, ease of administration and health-economic cost-benefits.

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