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Review paper

Which 5-fluorouracil regimen? — the great debate

Mark Vincent, Roberto Labianca[1] and Peter Harper[2]

London Regional Cancer Centre, Department of Medical Oncology, University of Western Ontario, London, Ontario N6A 4L6, Canada. [1]Unit of Medical Oncology, Ospedali Riuniti di Bergamo, 24100 Bergamo, Italy. [2]Guy's and St Thomas' NHS Trust, London SE1 9RT, UK.

5-Fluorouracil (5-FU) has been available for over 40 years and has been used in a wide variety of different regimens for the treatment of advanced colorectal cancer, a malignancy with a poor prognosis that is common in industrialized countries. However, despite numerous clinical trials in which 5-FU has been used alone and in combination with a variety of modulating agents [chiefly leucovorin (LV)], and has been administered by bolus injection and i.v. infusion, the optimal regimen for the management of advanced colorectal cancer remains unclear, and there are notable national and international variations in clinical practice. The toxicity of 5-FU also remains an obstacle to the achievement of overall clinical benefit in many patients. The introduction of novel chemotherapeutic agents may make it necessary to reassess the place of 5-FU in the treatment of advanced colorectal cancer. This article debates these issues with a review of clinical trials of 5-FU, and concludes that the future lies in the utilization of novel and established agents in combinations that may significantly improve outcomes, rather than in continuing experimentation with various schedules of 5-FU and LV. [© 1999 Lippincott Williams & Wilkins.]

Key words: Advanced colorectal cancer, 5-fluorouracil, regimens, treatment.

Introduction

Colorectal cancer is a major health problem in industrialized countries, with more than 300 000 new cases being diagnosed and in excess of 150 000 patients dying of the disease each year in the US and Europe.[1,2] Advanced disease is associated with a poor prognosis, with half the patients dying in approximately 1 year, whether they are treated or not.[3]

A significant minority of patients present with distant metastases or irresectable locoregional disease. In these patients, palliative surgery can prevent or minimize symptoms referrable to the primary tumor such as bleeding or obstruction. At some point, usually within 4 years of presentation, a further proportion will relapse, usually with distant metastases. Metastatic disease is only rarely curable with surgery; ultimately, around 40 of every 100 who develop the disease will die from it. Chemotherapy may be used to alleviate disease-related symptoms, to induce tumor regression/stabilization and to prolong patient survival. Radiotherapy is also used in advanced (especially rectal) disease to reduce tumor size before surgery, to treat symptomatic metastases and for palliation in patients in whom surgery is not possible. The extent to which all these treatments are used varies, particularly between Europe and the US.[4]

The fluoropyrimidine 5-fluorouracil (5-FU), introduced into clinical practice in the 1950s, remains the most widely used chemotherapeutic agent for the treatment of advanced colorectal cancer. The mechanism of action of 5-FU involves the inhibition of thymidylate synthase (TS), the enzyme that catalyzes the *de novo* formation of thymidine monophosphate (TMP) from deoxyuridine monophosphate (dUMP). TMP is subsequently converted to thymidine triphosphate (TTP), which is needed for DNA synthesis and repair (Figure 1). The conversion of dUMP to TMP requires the transfer of a methyl group from the reduced folate cofactor 5,10-methylenetetrahydrofolate to the 5-position of the uracil moiety. 5-FU is metabolized after entry into the cell via the facilitated uracil transport mechanism to 5-fluorodeoxyuridine monophosphate (FdUMP). In the presence of 5,10-methylenetetrahydrofolate, FdUMP forms a stable covalent complex with TS; this leads to eventual depletion of TTP and interference with DNA synthesis and repair.[5,6] 5-FU may also be converted to fluorouridine monophosphate (FUMP) by the sequential action of uridine phosphorylase and uridine kinase (or by the action of orotic acid phosphoribosyl transferase in the presence of 5′-phosphoribosyl-1-pyrophos-

Correspondence to M Vincent, London Regional Cancer Centre, Department of Medical Oncology, University of Western Ontario, London, Ontario N6A 4L6, Canada.
Tel: (+1) 519 685-8634; Fax: (+1) 519 685-8624;
E-mail: mvincent@lrcc.on.ca

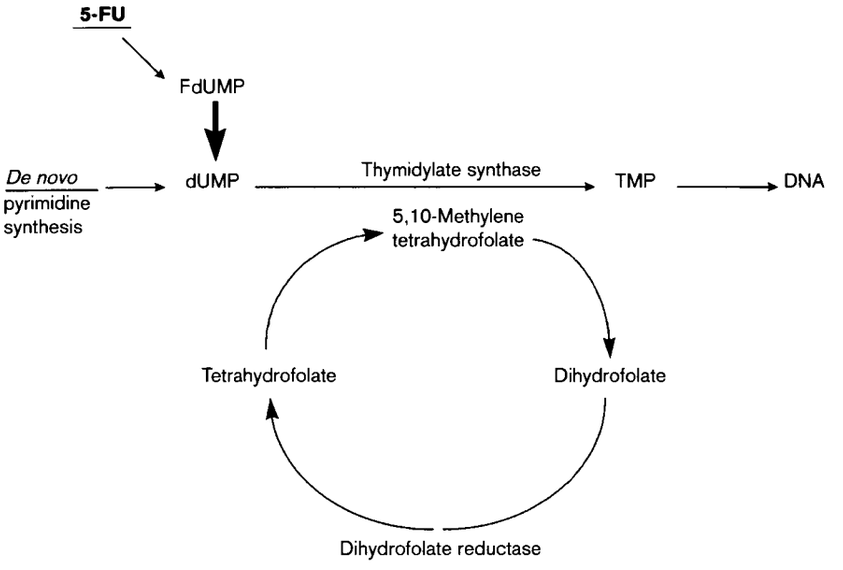

Figure 1. Site of action of 5-FU. Abbreviations: dUMP, deoxyuridine monophosphate; FdUMP, 5-fluorodeoxyuridine monophosphate; TMP, thymidine monophosphate.

phate). FUMP is then further metabolized to the triphosphate form (FUTP) which interferes with protein synthesis through incorporation into fraudulent RNA.

Although the theoretical basis for the antitumor effect of 5-FU in colorectal cancer is sound, tumor responses to bolus i.v. monotherapy in patients with advanced disease have been disappointing, with reviewers quoting overall response rates of only 10–15%.[4,7] This has led researchers to attempt to increase the antitumor activity of 5-FU through schedule modifications and the addition of biochemical modulators, the most interesting of which include folinic acid or leucovorin (LV), interferon (IFN)-α, methotrexate (MTX), *N*-phosphonacetyl-L-aspartate (PALA), hydroxyurea, dipyridamole and allopurinol. A proliferation of 5-FU-based regimens is to be found in the literature, the relative merits of which remain to be fully elucidated. The assessment of these regimens relative to each other is hindered by concerns over the definition and clinical usefulness of objective tumor response rates used in the majority of trials,[8] and a recent survey of the attitudes and practices of surgeons and oncologists has revealed substantial variations in the way in which advanced colorectal cancer is managed.[9] Response rates, patterns of toxicity, and cost and convenience of treatment vary widely according to the schedule of 5-FU administered and use of the cofactor LV, and inspection of the literature reveals much variation between and within countries in the choice of regimen with respect to schedule, method of administration (e.g. bolus versus infusion) and dosage. Indeed, the regimen received by the patient appears to depend as heavily on the country in which they are being treated as on any other factor. In addition, the duration of palliative chemotherapy varies widely: 5-FU does not have a cumulative dose limit and it is standard practice in some countries to continue treatment in patients with advanced disease until there is evidence of disease progression.

The development of several novel agents including 5-FU analogs (ftorafur, doxifluridine, uracil-tegafur) and innovative compounds such as irinotecan (CPT11), oxaliplatin, capecitabine, multitargeted antifolate (MTA) and the direct TS inhibitor raltitrexed has increased the need for standardized efficacy measurements in advanced colorectal cancer and effective evaluation of the evidence already available from clinical trials. This is particularly important when it is claimed that other treatments may offer tolerability, patient preference and cost advantages.[10–12] These concerns have been addressed recently by the European Organization for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group (GITCCG), which has considered the introduction of new drugs and the definition of novel patient benefit endpoints.[13]

Table 1. Studies published from 1989 on (with key studies published before that year) that assessed 5-FU regimens in patients with advanced colorectal cancer: overall response rates (%) and median survival times are shown for relevant regimen(s) for each study; studies are phase III unless stated otherwise; see footnotes and text for clarification of regimens

Reference (no. evaluable patients)	Regimen[a]						Comments
	5-FU alone	Mayo	Machover	Weekly 5-FU + HDLV	de Gramont	CI	
Aranda *et al.*[30] (104)[b]						37.5% 14.5 months	Median TTP = 7.4 months.
Beerblock *et al.*[31] (98)[b]						33.7% 10 months	Regimen included HDLV (1 g/m^2 every 2 weeks). Median TTP = 8 months.
Blijham *et al.*[32] (297)						11% 9.3 months	Significantly higher OR (23%; $p=0.025$) and trend to increased survival (12.4 months) when MTX added to this regimen.
Bobbio-Pallavicini *et al.*[23] (146)[c]	10.2% 6 months		31.9% 8 months				Differences significant ($p<0.01$ for OR and $p<0.05$ for survival) between treatments.
Buroker *et al.*[33] (362)		35% 9.3 months		31% 10.7 months			No significant difference in progression-free survival ($p=0.74$). Lower costs and toxicity with Mayo regimen.
Caudry *et al.*[34] (129)				25% 9.6 months		45.8% 12.9 months	Median TTP 8 (CI) versus 4.4 (weekly 5-FU + HDLV) months. Significant difference for TTP and survival ($p=0.0026$ and 0.028). Borderline response significance ($p=0.048$). Additional arm with 5-FU CI + cyclophosphamide and mitomycin-C terminated early because of toxicity.
Corfu-A Study Group[35] (492)[c]			18% 11.3 months				Comparison with 5-FU + IFN-α-2a (Wadler *et al.*[36]). Similar rate and duration of response and survival with both regimens.
de Gramont *et al.*[37] (433)		14.4% 13.1 months			32.6% 14.3 months		Less grade 3–4 toxicity with de Gramont. Significant difference in OR ($p=0.0004$). Median TTP 22 (Mayo) versus 27.6 weeks ($p=0.0012$).
Di Costanzo *et al.*[28] (155)	18% 14.3 months		16% 12.2 months				Median TTP = 20 and 21 weeks for 5-FU with and without LV, respectively. No significant differences between treatments.
Erlichman *et al.*[22] (125)[c]	7% 9.6 months		33% 12.6 months				5-FU + LV significantly more effective: $p<0.0005$ for response, $p=0.05$ for survival and $p=0.023$ for TTP (5.1 versus 2.9 months).
Hanna *et al.*[38] (85)[d]					10.6% 6 months		Median duration of response = 11 months.
Hansen *et al.*[25] (477)	18% 10.4 months					28% 13.0 months	Weekly cisplatin added to each 5-FU regimen in two further arms. Better OR ($p=0.45$) and TTP (6.2 versus 5.1 months; $p=0.007$) with infusion. No advantage associated with addition of cisplatin.

continued

Table 1. Continued

Reference (no. evaluable patients)	Regimen[a]						Comments
	5-FU alone	Mayo	Machover	Weekly 5-FU + HDLV	de Gramont	CI	
Hill *et al.*[39] (155)						33% 11.7 months	Median TTP = 193 days. IFN-2α added in second treatment arm. No significant differences in efficacy, but more toxicity with IFN-2α.
Jäger *et al.*[40] (291)				21.6% 12.7 months			Median TTP = 29.3 weeks. No significant differences from weekly 5-FU + LDLV (OR 17.5%; survival 54.1 weeks; TTP 30 weeks).
Köhne *et al.*[41] (230)						44% 16.2 months	5-FU + LV. Median TTP = 7.1 months. OR, TTP and survival significantly better than with 5-FU + IFN-α-2b. 5-FU + LV + IFN arm terminated early because of toxicity.
Labianca *et al.*[17]	10% 11 months		20.6% 11.5 months				OR significantly better ($p=0.046$) with 5-FU + LV; no significant difference in survival.
Leichman *et al.*[21] (599)[b]	29% 14 months	27% 14 months		21% 13 months		29% 15 months	Seven regimens tested (full details in Table 2). Positive survival trend in favor of unmodulated 5-FU. More high-grade toxicity with bolus regimens.
Lokich *et al.*[20] (174)	7% 11 months					30% 10 months	Significant difference in OR ($p<0.001$), but not survival.
Machiavelli *et al.*[26] (118)	12% 8.3 months						Response better with sequential regimen of MTX, 5-FU and LV (28%; $p=0.049$), but no significant difference in survival (11.2 months; $p=0.25$).
Machover *et al.*[42] (86)[b]			33%				5-FU 340-400 mg/m^2. Median survival = 19.5 months and TTP = 10 months for responders.
O'Connell[18] (208)[c,e]	10%	43%	26%				Tumor response: both LV regimens superior ($p<0.05$) to 5-FU alone. Survival and TTP also better with LV regimens ($p \leqslant 0.03$).
Petrelli *et al.*[27] (65)	11% 11 months			48% 12 months			Roswell Park Memorial Institute. OR 5% and survival 10 months with 5-FU + MTX. $p=0.0009$ between groups for OR, but no significant difference in survival.
Petrioli *et al.*[19] (185)	18.6% 7.5 months		33.3% 13.5 months				5-FU + LV given every 3 weeks. p between treatments <0.045 for OR and <0.039 for survival. Slightly more toxicity with 5-FU + LV.
Poon *et al.*[43] (457)[c]		42% 12.7 months	31% 12.7 months				Both regimens significantly ($p \leqslant 0.01$) more effective than methotrexate + 5-FU + LV.
Recchia *et al.*[44] (97)			40% 13.3 months				Better OR than with 5-FU and HDLV + IFN-α-2b (26%). No significant difference in times to treatment failure and survival.

continued

Table 1. Continued

Reference (no. evaluable patients)	Regimen[a]					Comments
	5-FU alone	Mayo	Machover	Weekly 5-FU + HDLV	de Gramont CI	
Seymour *et al.*[45] (205)					27% 10 months	Comparison with de Gramont regimen + IFN-α-2a. No significant differences between treatments.
Scheithauer *et al.*[46] (135)		19% 12.6 months				No significant difference between these and figures for 5-FU + LDLV with cisplatin.
Valone *et al.*[29] (249)	17.3% 11.3 months		18.8% 10.7 months			Combination of MTX, 5-FU and oral LV also included. No significant differences between regimens. Median TTP = 166 days with 5-FU + LV and 138 days with 5-FU alone.
Weh *et al.*[47] (57)				9% 8 months		All patients previously treated and with progressive disease.

[a]Machover regimen: 5-FU 400 mg/m^2 + LV 200 mg/m^2 for 5 days every 4–5 weeks. Mayo regimen: 5-FU 425 mg/m^2 + LV 20 mg/m^2 for 5 days every 4–5 weeks. De Gramont regimen: LV 200 mg/m^2 over 2 h, then 5-FU 400 mg/m^2 bolus + 400 or 600 mg/m^2 i.v. infusion over 22 h, repeated on day 2, every 2 weeks.
[b]Phase II trial.
[c]Modified Machover regimen (5-FU 370 mg/m^2 + LV 200 mg/m^2 every 4–5 weeks).
[d]Retrospective data.
[e]Modified Mayo regimen (5-FU 370 mg/m^2 + LV 20 mg/m^2 every 4–5 weeks).
Abbreviations: CI, continuous infusion; HDLV, high-dose leucovorin; LDLV, low-dose leucovorin, MTX, methotrexate; OR, objective response rate (complete + partial tumor responses).

This review will therefore:

- Examine and contrast those 5-FU-based treatments most commonly reported in recent years.
- Seek to determine whether there is any substantial clinical advantage associated with any particular regimen in patients with advanced colorectal cancer.

Considerations in the choice of 5-FU regimen

The primary consideration in the choice of any treatment for any disorder is clearly that of efficacy and an accurate evaluation of primary response has traditionally been considered to be of major importance in chemotherapy for advanced cancer. The efficacy of chemotherapy for colorectal cancer has often been judged by the so-called objective response (or regression), usually defined as a reduction in measurable tumor mass of at least 50%.[8] However, such responses may not be of much value clinically because they are usually brief and offset by drug toxicity associated with continuous treatment. In addition, measurements of intra-abdominal disease tend to be imprecise, even with the latest imaging techniques, and there is no necessary correlation between rates of objective response and improvements in survival or quality of life.[8] Of much more value as an indicator of the efficacy of a chemotherapy regimen is the complete response rate, as a substantial rate of complete and durable response is an important precondition for any regimen's curative potential. Furthermore, the most important indicator of the quality of a complete remission is the relapse-free survival from the time all treatment is discontinued.[14]

Other considerations in the selection of a treatment regimen are those that relate to tolerability and effects on a patient's quality of life. The burden to the patient of cytotoxic chemotherapy is a major factor influencing treatment, and includes not only the adverse effects of the drugs themselves but also other contributory factors such as psychological distress, social isolation, loss of time to participate in pleasurable activities, financial difficulties and hospital stays. When there is little or no prospect of a cure (as in advanced colorectal cancer), this choice may be more difficult, although some improvement in symptom control can be achieved through reduction in tumor bulk in these patients.[15] Patient preference is likely to have a considerable influence in future decisions as to which chemotherapy regimens are to be used and was shown in a recent study to be influenced to a large extent by the effect of treatment on patients' lifestyles.[12]

Overall, the benefits of a cancer treatment regimen should outweigh its cost in terms of patient suffering. Quality of life considerations are valuable in the selection of regimens and the conduct of clinical trials, although they do not replace traditional endpoints (particularly complete response and survival) or data based on physician reports of toxic effects.[16] Related to quality of life are those issues associated with the convenience of the regimen for patients, and the practicalities of attendance for treatment and simplicity or otherwise of administration.

5-FU-based regimens in current use: key clinical trials

Bolus 5-FU alone

Despite apparent methodological consistency in the assessment of tumor response, reports in the literature show a wide variety of regimens based on 5-FU, with inconclusive efficacy results and no clear indication of which, if any, are superior. Tables 1 and 2 contain data from a number of comparative studies involving unmodulated 5-FU. In several of these, a dosage of 400–500 mg/m^2 daily for 5 days every 4–5 weeks was used,[17–21] but this was by no means universal. Erlichman *et al.*[22] Bobbio-Pallavicini *et al.*[23] and Doroshow *et al.*[24] used a lower starting dosage (370 mg/m^2 per day), whereas Hansen *et al.*[25] gave 500 mg/m^2 daily for 5 days, then 600 mg/m^2 every week from week 3 onwards. Other regimens were 1200 mg/m^2 every 15 days,[26] 450 mg/m^2 daily for 5 days followed by 200 mg/m^2 on alternate days for six doses,[27] 13 mg/kg daily for 5 days every 4 weeks[28] and 12 mg/kg daily for 5 days followed by 15 mg/kg per week.[29] Overall response rates (complete and partial responses) with unmodulated bolus 5-FU ranged from 7 to 29% and median survival from 6 to 14 months with these regimens, although only one trial yielded a response rate of over 20%.[21] This was a phase II screening study in which no substantial advantage was shown for any of seven regimens (see Table 2 for details).

Bolus 5-FU modulated with LV

Disappointment with response rates and survival with unmodulated 5-FU has led to attempts to improve the activity of this drug with various other agents as mentioned earlier. The current standard treatment for advanced colorectal cancer is generally 5-FU modulated with LV, the rationale behind which is as follows: the stability of the ternary complex formed by the false

Table 2. Studies assessing 5-FU regimens not covered by those listed in Table 1 (doses are intravenous bolus or rapid infusion unless stated otherwise)

Reference (no. evaluable patients)	Regimens	OR (%)	Median survival	Comments
Ardalan *et al.*[48] (22)	5-FU 2600 mg/m^2 + LV 500 mg/m^2 CI × 24 h each week	45		OR 58% in previously untreated patients (n = 12). Median survival not reached in these patients at 22 months; 10 months for previously treated patients.
Goldberg *et al.*[49] (514)	LV (6S isomer) 100 mg/m^2 + 5-FU 370 mg/m^2 d1–5 every 4 weeks to week 8, then 5-weekly	28		Comparison of three LV formulations. No statistically significant differences in response rate, survival or toxicity between regimens.
	Oral LV (racemic mixture) 125 mg/m^2 at h 0, 1, 2 and 3 + 5-FU 370 mg/m^2 at h 4 d1–5 every 4 weeks to week 8, then 5-weekly	34		
	LV (racemic mixture) 200 mg/m^2 + 5-FU 370 mg/m^2 d1–5 every 4 weeks to week 8, then 5-weekly	34		
Leichman *et al.*[21] (599)	5-FU 500 mg/m^2 × 5 d 5-weekly	29	14 months	Phase II data. No regimen showed substantial improvement over 5-FU bolus of single-agent therapy for either response or survival in metastatic colorectal cancer. Major high-grade toxicities were granulocytopenia and diarrhea, and were more frequent with bolus 5-FU. Most encouraging results overall seen with infusion regimens.
	LV 20 mg/m^2 + 5-FU 425 mg/m^2 × 5 d 4-weekly × 2 cycles, then 5-weekly	27	14 months	
	LV 500 mg/m^2 + 5-FU 600 mg/m^2 weekly × 6 weeks every 8 weeks	21	13 months	
	5-FU 300 mg/m^2/d CI × 28 d every 5 weeks	29	15 months	
	5-FU 200 mg/m^2/d CI × 28 d every 5 weeks + LV 20 mg/m^2 d1,8,15 and 22	26	14 months	
	5-FU 2600 mg/m^2 CI × 24 h each week	15	15 months	
	PALA 250 mg/m$^{2/}$ + 5-FU 2600 mg/m^2 CI × 24 h each week	25	11 months	
Labianca *et al.*[50] (422)	LV (6*S* isomer) 100 mg/m^2 + 5-FU 370 mg/m^2 d1–5 every 4 weeks	9.3		TTP = 8 months in both groups. No significant differences between groups for OR, Kaplan–Meier survival curves, TTP or toxicity.
	LV (6*S* isomer) 10 mg/m^2 + 5-FU 370 mg/m^2 d1–5 every 4 weeks	10		
Laufman *et al.*[51] (198)	5-FU 375 mg/m^2/d × d1–3 + LV 100 mg/h × 4 h, then 100 mg every 4 h × 72 h; then 5-FU 375 mg/m^2 weekly with dose escalation + LV 100 mg/h × 4 h and then every 4 h for 24 h	32		No significant differences in OR, Kaplan–Meier survival curves or TTP.
	5-FU as above with placebo	23		

continued

Table 2. Continued

Reference (no. evaluable patients)	Regimens	OR	Median survival	Comments
Doroshow *et al.*[24] (76)	5-FU 370 mg/m^2/d × 5 d every 28 d As above + LV 500 mg/m^2/d from 24 h before 5-FU to 12 h afterwards	13% 44%	386 days (12.7 months) 432 days (14.2 months)	Median TTP or death = 164 (5-FU + LV) versus 120 (5-FU alone) days (p=0.45). p=0.0019 between groups for OR but no significant difference for survival.

Abbreviations: CI, continuous infusion; OR, objective response (complete + partial tumor responses).

substrate FdUMP with TS is dependent on intracellular levels of 5,10-methylene dihydrofolate. Depletion of intracellular folate pools may result in incomplete or short-lived ternary complex formation. LV stabilizes the inactive FdUMP/TS/5,10-methylene dihydrofolate complex, and increases the extent and duration of 5-FU-mediated TS inhibition (reviewed by Grem).[52]

The popularity of 5-FU+LV increased during the 1980s, and peaked with work carried out at the Mayo Clinic in the US that showed a monthly regimen of 5-FU bolus once daily (425 mg/m^2) with low-dose LV (20 mg/m^2) to apparently prolong survival and time to disease progression (TTP), to improve quality of life, and to increase tumor response rates compared with 5-FU alone.[53] At around the same time, Machover *et al.*[54] were demonstrating good activity of a similar regimen with 5-FU 370–400 mg/m^2 and high-dose LV (200 mg/m^2), and the Roswell Park Memorial Institute in Buffalo was developing a weekly regimen of high-dose LV (500 mg/m^2 as a 2 h infusion) and 5-FU (600 mg/m^2 i.v. bolus at mid-infusion), with both drugs being given weekly for 6–8 weeks.[55] However, there are several variations of the weekly regimen, including LV 500 mg/m^2 with 5-FU 500 mg/m^2,[40] and there has been some experimentation with formulations of the active levorotatory 6*S* isomer of LV (Table 2).[49,50]

A meta-analysis of nine randomized trials in 1381 patients showed significant benefit in terms of tumor response rate of 5-FU with LV compared with 5-FU alone.[56] The analysis covered a range of different regimens and showed overall tumor response rates to be significantly higher when LV was added to 5-FU (23 versus 11%; response odds ratio 0.45; $p<10^{-7}$). However, overall survival was similar for unmodulated and modulated 5-FU (survival odds ratio 0.97; p=0.57). These observations are concordant with the results of many of the trials discussed in the present review, in which improvements in tumor response with modulated 5-FU were not matched by corresponding statistically significant improvements in survival.

Continuous infusion of 5-FU

Administration of 5-FU by i.v. infusion has evolved from experimental observations of the schedule dependency of this agent, and technological developments in the last 20 years that have led to the availability of reliable and safe ambulatory drug administration systems. These schedules have been developed as a possible means of increasing dose intensities of 5-FU and increasing proportions of tumor cells exposed to the drug during S phase. Interest in

administration of 5-FU by infusion has also been prompted by concerns over the toxicity seen when the drug is given as a bolus injection and by a realization that substantial increases in 5-FU dose intensity with bolus regimens are not possible without unacceptable increases in levels of toxicity.

Infusion regimens vary widely, but fall into two basic groups: those that involve long-term continuous infusion of 5-FU and those that involve intermittent shorter infusions (typically over 24–48 h). Continuous infusion schedules involve the long-term use of ambulatory infusion equipment, and intermittent infusions can be seen as a compromise to offer the increases in dose intensity and postulated differences in mechanism of action of 5-FU[57] associated with infusion regimens without the need for ongoing administration, which typically continues for 8–12 weeks.[58]

Four major types of 5-FU infusion may be identified in the literature. The first is the long-term continuous infusion of 300 mg/m^2 per day as used in the US by Lokich *et al.*[20] The French regimen devised by de Gramont *et al.*[37] involves the 2-weekly administration of a 22 h infusion of 5-FU after an initial 5-FU bolus modulated by a 2 h infusion of LV, repeated on day 2.[37] Two other intermittent infusion regimens have been developed in Europe: a Spanish schedule that involves once weekly 48 h infusions of 5-FU with modulation with oral LV[30] and a 24 h infusion regimen modulated with LV that has been developed in Germany.[41] These regimens of 5-FU (except for the de Gramont regimen: see footnote to Table 1 for details), together with other variations, are detailed in Table 3.

Median survival data from trials in which infusions of 5-FU were used are summarized in Figure 2, from which it may be seen that no clear survival trends are apparent for any particular type of regimen. The original phase III trial in which infused 5-FU was compared with a bolus regimen was published in 1975.[59] In this comparison, a dose intensity approximately 2.5 times that in the bolus arm was achieved with infusion (30 mg/kg per day for 5 days versus bolus 12 mg/kg per day). Response rates were substantially different in favor of the infusion (22 versus 44%), but the authors stated that this difference was explained at least in part by differences in patient characteristics between the two treatment groups.

Various results have been reported in more recent trials (Tables 1 and 2). Caudry *et al.*[34] reported significant improvements over a weekly 5-FU + high-dose LV regimen in terms of overall response and median survival with their 21 day infusion regimen (Table 3). Other researchers have shown significant improvements over bolus regimens in overall response, but not median survival, with continuous infusion.[20,25] However, analysis of tails of survival curves from one of these trials (that carried out by the Mid-Atlantic Oncology Program),[20] in which patients with bidimensionally measurable metastatic disease were randomized to either 5-FU 500 mg/m^2 by i.v. bolus daily for 5 days every 5 weeks or 5-FU 300 mg/m^2 per day by continuous i.v. infusion, showed a modest non-significant trend towards improved survival after 18 months with 5-FU infusion.

Recent meta-analysis data from six randomized trials (n=1219) in which 5-FU i.v. bolus was compared with continuous i.v. infusion indicate an advantage for the

Table 3. Summary of 5-FU infusion regimens used in studies shown in Tables 1 and 2

Study	Infusion regimen
Aranda *et al.*[30] (48 h infusion)	5-FU 2 g/m^2/48 h once-weekly + oral LV 60 mg/kg every 6 h
Ardalan *et al.*[48] (24 h infusion)	5-FU 2600 mg/m^2 + LV 500 mg/m^2 CI (24 h each week)
Beerblock *et al.*[31] (48 h infusion)	5-FU 1.5–2 g/m^2/d over 48 h every 2 weeks after LV 500 mg/m^2/d × 2 d
Blijham *et al.*[32] (48 h infusion)	5-FU 60 mg/kg/48 h weekly × 4 weeks, then 2 weekly × 4 weeks, then 3 weekly
Caudry *et al.*[34] (protracted infusion)	5-FU 400 mg/m^2/d for 21 of every 28 days
Hansen *et al.*[25] (protracted infusion)	5-FU 300 mg/m2/d
Hill *et al.*[39] (protracted infusion)	5-FU 300 mg/m^2/d × 10 weeks, then 2 weeks off, then × 10 further weeks
Köhne *et al.*[41] (24 h infusion)	5-FU 2600 mg/m^2 × 24 h each week + LV 500 mg/m2 5-FU 2600 mg/m2 × 24 h each week + IFN-α-2b 3 × 10^6 U × 3 week before 5-FU 5-FU + LV + IFN-α-2b
Leichman *et al.*[21] (protracted and 24 h infusions)	5-FU 300 mg/m^2/d × 28 d every 5 weeks 5-FU 200 mg/m^2/d × 28 d every 5 weeks + LV 20 mg/m^2 d1,8,15,22 5-FU 2600 mg/m^2 × 24 h each week
Lokich *et al.*[20] (protracted infusion)	5-FU 300 mg/m^2/d × 10 weeks

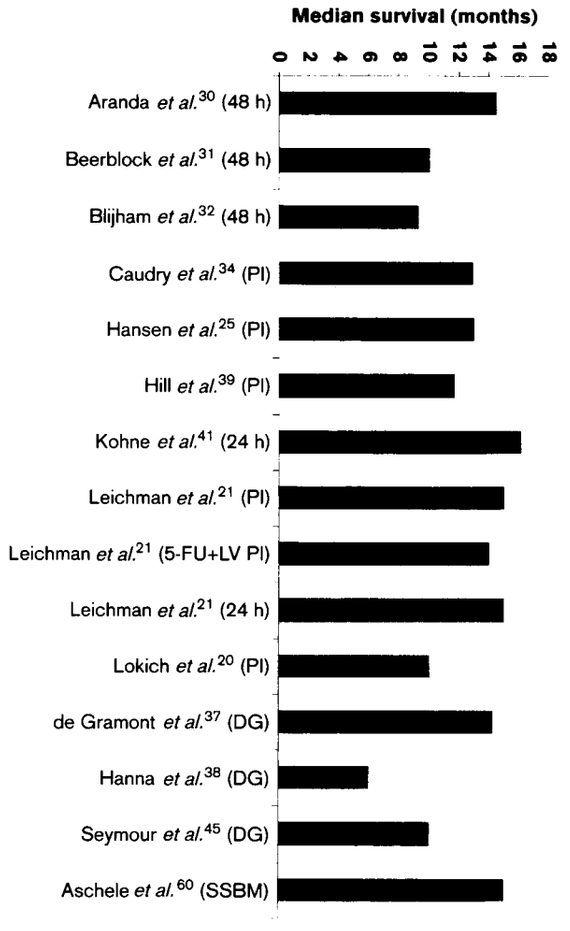

Figure 2. Median survival in trials in which 5-FU was administered as a continuous infusion. Details of regimens used are shown in Table 3 (except de Gramont and SSBM). Regimens consist of 5-FU alone unless stated otherwise. Abbreviations: 24 h, 24 h infusion; 48 h, 48 h infusion; DG, de Gramont; SSBM, schedule-selective biochemical modulation involving bolus and infusional 5-FU with methotrexate and interferon or LV (see text for details); PI, protracted infusion.

latter type of regimen.[61] Tumor response rates (22 versus 14%; p=0.0002) were significantly better with continuous infusion than with bolus administration and an improvement in survival was also reported (overall hazard ratio 0.88; p=0.04). Multivariate analysis showed treatment and performance status to be the only two significant predictors of tumor response, whereas survival was predicted additionally by primary tumor site (patients with rectal cancer tended to fare better). In addition, pooled analysis of phase II data (five trials; n=140) has indicated that continuous infusion of 5-FU may be of value as second-line therapy in patients who have failed to respond to modulated bolus regimens.[62] One complete response and 15 partial responses were observed (overall response rate of 11%), with stabilization of disease in 38% of patients. Median survival was 7.7 months, with a median TTP of 4.6 months. None of the inclusion parameters used across the trials were found to predict response to treatment, although associations were reported between performance status and survival duration and TTP.

Reports are also available to show some success with the bimonthly two-stage infusion regimen with high-dose LV that has been developed by de Gramont *et al.* One of these trials was a comparison of the bimonthly infusion with the Mayo regimen (Table 1).[37] As with many of the other comparisons of 5-FU-based therapy discussed above, significant improvements in overall response rate and TTP with the bimonthly regimen were not matched by improvements in median survival, although these results may have been affected by crossover of patients in both treatment arms to second-line continuous infusion 5-FU therapy at disease progression. However, there were differences in toxicity between the two regimens: the Mayo regimen was associated with more frequent grade 3 to 4 neutropenia (7.3 versus 1.9%; p=0.0052), diarrhea (7.3 versus 2.9%; p=0.039) and stomatitis (12.7 versus 1.9%; p=0.0001) than the de Gramont regimen. Overall, 23.9 and 11.1% of patients who received the Mayo and de Gramont regimens, respectively, experienced grade 3 to 4 toxicity; this difference between groups was highly statistically significant (p=0.0004). A recent review by the authors of this study has stated the opinion that improvement of objective response with acceptable levels of toxicity is possible through the use of higher doses of 5-FU administered by continuous infusion.[63] There is evidence that after the establishment of the de Gramont regimen as control arm in various phase III studies, response rates initially observed[64] have fallen.

Schedule-specific biochemical modulation (SSBM)

Some authors have suggested that SSBM of 5-FU is beneficial in advanced colorectal cancer. Interim data are available from a phase III study in 130 evaluable patients in which (i) two biweekly cycles of bolus 5-FU (600 mg/m^2) modulated with methotrexate (200 mg/m^2 given 24 h before 5-FU) with LV rescue, alternating with 5-FU by continuous infusion (200 mg/m^2 daily for 3 weeks) modulated with low-dose 6S-LV (10 mg/m^2 weekly bolus) was compared with (ii) a control regimen consisting of biweekly cycles of bolus 5-FU

(600 mg/m^2) modulated with methotrexate (200 mg/m^2 given 24 h before 5-FU) with LV rescue.[65] Overall response rates were 41.5% (6.2 % complete response) and 13.8% (1.5% complete response) in the SSBM and control groups, respectively.

A further study[60] examined a regimen consisting of two biweekly cycles of bolus 5-FU (600 mg/m^2) modulated with methotrexate (200 mg/m^2 given 24 h before 5-FU) and IFN-β (four 12 h intramuscular doses of 3×10^6 IU started at the same time as 5-FU), alternating with 5-FU by continuous infusion (200 mg/m^2 daily for 3 weeks) modulated with 6*S*-LV (20 mg/m2 weekly bolus). After a 1 week rest, the entire 8 week cycle was repeated if indicated. Five complete and 17 partial responses were recorded (41% overall response rate) in 54 evaluable patients. Median survival is shown in Figure 2. The overall median time to treatment failure was 15.0 months.

Which 5-FU regimen?

Despite enormous efforts on the part of the oncological community to determine the optimal dosage and schedule of 5-FU over the past 40 years and the publication of large numbers of studies with variations on numerous regimens, there is still no clear 'gold standard' for the chemotherapeutic management of patients with advanced colorectal cancer. The available literature indicates the Mayo regimen of monthly bolus 5-FU with low-dose LV to be the reference standard for new agents and other regimens based on 5-FU with LV; nevertheless, many patients experience considerable toxicity.

In spite of the apparent improvements in response rates seen with 5-FU+LV, the clinical use of these regimens is still hampered by conflicting survival data and a lack of consensus over optimum schedules and dosages. As can be seen from the literature summarized earlier, there is no clear indication of which, if any, of the many reported regimens is the best. Controversy surrounding high and low dosages of LV has also been a feature of modulated 5-FU therapy in advanced colorectal cancer for many years because of a lack of conclusive data to show a clear advantage for either type of regimen. A pivotal clinical trial that compared the increasingly popular Mayo (5 day bolus 5-FU with low-dose LV) and Machover (5 day bolus 5-FU with high-dose LV) regimens in the early 1990s indicated low-dose LV (20 mg/m^2) to be as active as high-dose LV (200 mg/m^2) in terms of both response rate and survival[43] (Table 1 and Figure 3). These observations, together with the potential cost savings associated with lower dosages of LV, have led to the adoption of the Mayo regimen as standard therapy in many institutions. Nevertheless, the trials summarized in Table 1 show a wide variation in response rates and median survival times for both Mayo and Machover regimens (14.4–43% and 9.3–14 months versus 16–40% and 8–13.5 months, respectively). These ranges appear to corroborate the similarity in activity between these regimens reported by the Mayo Clinic.

Toxicity of 5-FU

If 5-FU is administered at schedules that are sufficiently aggressive to confer clinical benefit, many patients experience stomatitis, diarrhea or leucopenia as dose-limiting adverse effects.[66] Despite its widespread acceptance, the full-dosage Mayo schedule is associated with significant morbidity in many patients. A recent retrospective analysis of 160 patients treated in this way from 1990 to 1997 showed that 35% were unable to receive their second cycle of 5-FU + LV as scheduled because of toxicity during the first cycle, that 79% required dosage reduction and that 11% discontinued therapy because of the toxicity of the regimen (two patients died as a result of this). The authors concluded that the proportion of patients who received their full scheduled dosage of 5-FU + LV at the second cycle was less than that which would be deemed acceptable in current phase I trials and that known clinical characteristics of patients do not clearly predict toxicity with 5-FU.[67]

Individual major studies of the full-dosage Mayo regimen[33,43] have shown high levels of toxicity, with Buroker *et al.*[33] reporting the need for hospitalization in 21% of patients. In addition, the lower dosages of 5-FU used in the Machover regimen do not appear to attenuate toxicity when they are administered with the high dosage of LV required in this regimen. The incidence of severe leucopenia with this regimen (28%) was the same as that with the Mayo regimen in the Mayo Clinic study.[43] Toxicity of this nature is especially pertinent in patients with advanced colorectal cancer, because the large majority who are treated in this way will be expected to obtain palliation rather than a cure. The overall benefit to the patient of these regimens is likely to be questionable if the dosages used cause serious impairment of quality of life.

In a recent randomized study, survival benefit from both the 5-FU + LV and the 5-FU arms was found to be strongly associated with the development of toxicity, especially stomatitis and diarrhea.[68] For 5-FU+LV, patients survived approximately 3 months longer if they developed WHO grade 2 or greater stomatitis (p=0.04) and approximately 4.4 months longer if they

developed WHO grade 2 or greater diarrhea (p=0.06). These results imply that survival benefit with 5-FU bolus regimens cannot be uncoupled from toxicity.

It should also be noted that catastrophic and potentially fatal adverse effects are possible with 5-FU in patients with inherited dihydropyrimidine dehydrogenase (DPD) deficiency.[69] These patients are unable to metabolize and clear fluoropyrimidines adequately. They represent a small proportion of the patient population in whom the use of 5-FU may be life-threatening and who cannot be readily identified under usual clinical circumstances. In addition, some patients are heterozygous for DPD deficiency and may exhibit severe but not catastrophic toxicity; more work is needed to clarify the situation with these patients. It should also be noted that levels of DPD are rate limiting for the catabolism of 5-FU. As DPD can be saturated by 5-FU and because levels of this enzyme vary widely across populations, toxicity due to accumulation of 5-FU is both highly variable and unpredictable.

Infusion versus bolus

The concept of infusional administration of 5-FU as an optimal administration method has evolved from the observation that 5-FU is a S-phase-specific agent with a short half-life that limits cell exposure time and from the development of infusion pump technology that has made possible the safe and effective delivery of this drug in an ambulatory

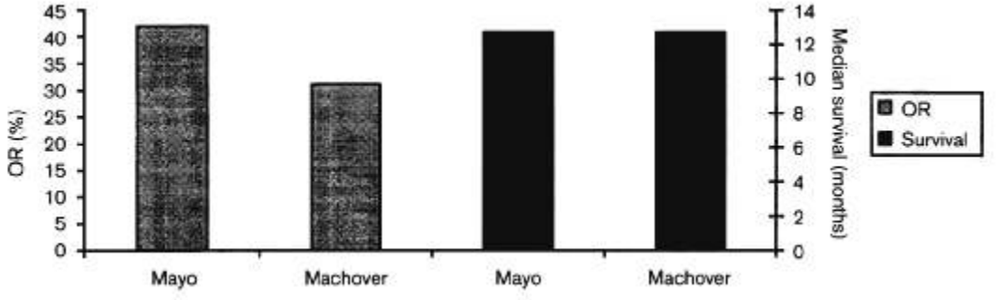

Figure 3. Overall tumor responses (OR; complete and partial responses) and median survival with 5-FU 425 mg/m^2 i.v. bolus + LV 20 mg/m^2 (Mayo regimen; n = 89) or 5-FU 370 mg/m^2 i.v. bolus + LV 200 mg/m^2 (modified Machover regimen; n = 81) daily for 5 days every 4–5 weeks (Poon *et al.*[43]).

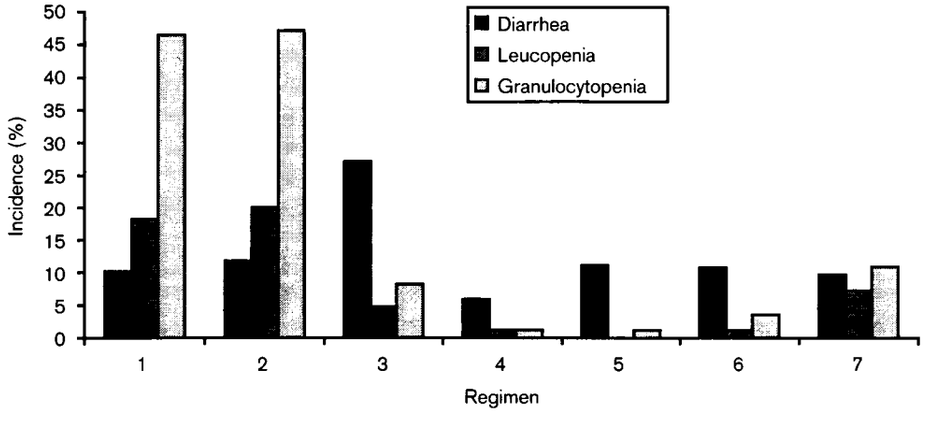

Figure 4. Incidence of grade 3–4 (severe) diarrhea and hematological toxicity in patients who participated in the phase II comparison of seven 5-FU-containing regimens carried out by the Southwest Oncology Group (Leichman *et al.*[21]). Regimens were as follows: (1) 5-FU 500 mg/m^2/day bolus for 5 days every 5 weeks; (2) 5-FU 425 mg/m^2 bolus + LV 20 mg/m^2 daily for 5 days every 4 weeks for two cycles, then 5-weekly; (3) 5-FU 600 mg/m^2 bolus + LV 500 mg/m^2 weekly for 6 weeks every 8 weeks; (4) 5-FU 300 mg/m^2/day continuous infusion for 28 days every 5 weeks; (5) 5-FU 200 mg/m^2/day continuous infusion for 28 days every 5 weeks + LV 20 mg/m^2 on days 1, 8, 15 and 22; (6) 5-FU 2600 mg/m^2 continuous infusion for 24 h each week; (7) 5-FU 2600 mg/m^2 continuous infusion + PALA 250 mg/m^2 for 24 h each week.

setting. Two main features distinguish all the infusion schedules from the bolus schedules: different toxicities are reported and much higher total doses of 5-FU are possible with continuous infusions. A review of preclinical and clinical literature on the antitumour and toxic effects of 5-FU has indicated that the drug appears to work in different ways when given by bolus injection or continuous infusion.[57]

Paradoxically, bolus regimens that are more convenient for patients and clinics alike tend to be more toxic than their more inconvenient infusional counterparts. This was shown by the marked differences in toxicity in the phase II comparison of seven regimens that was carried out by the Southwest Oncology Group (Figure 4).[21] Higher grades of hematological toxicity were seen in the bolus arms than in the infusion arms of the trial. Grade 3–4 granulocytopenia was seen in 47% of patients who received bolus 5-FU with or without LV modulation (regimens 1 and 2). In contrast, only 1% of patients who received continuous infusion regimens 4 and 5 experienced grade 3–4 granulocytopenia. Grade 3–4 diarrhea was seen most frequently in patients who received a weekly bolus of 5-FU with high-dose LV (27%; regimen 3).

Overall, the evidence available indicates that, regardless of the schedule used, bolus administration of 5-FU is associated with leucopenia, stomatitis and diarrhea, whereas infusions are complicated by stomatitis and dermatitis. Achievable dose intensities appear to be approximately 4 times higher with continuous infusion of 5-FU than with bolus administration, but this has not resulted to date in any survival advantage relative to bolus administration of 5-FU for these regimens. Toxicities and achievable dose intensities appear to be similar for all infusion regimens, whether 5-FU is given for 24 h each week,[21,30–32,37,41] or by protracted infusion,[20,21,25,34,39] and no substantial improvements in survival have yet been reported with any particular infusion regimen relative to others.

As noted earlier, continuous infusion regimens have become possible because of advances in ambulatory i.v. delivery systems. However, there is concern over the technical complexity associated with these delivery systems,[70] and other problems such as the risk of infection associated with indwelling lines. Patient preference and quality of life considerations may also affect the uptake of infused 5-FU regimens: continuous infusion was the least popular of four regimens in a patient preference study by Topham[12] because of the need for an indwelling Hickman line; many patients felt this to be an unacceptable burden of treatment.

Adapting dosages and schedules of 5-FU

The reason for the selection of 425 mg/m^2 per day as a 5 day dosage of bolus 5-FU with low-dosage LV is not clear from the literature. Some centers have attempted to minimize toxicity through the use of modified regimens and reduced starting dosages of 5-FU, but there is no clear evidence that this is of any clinically significant benefit, and introduces the risk that suboptimal dosages may be given to some patients. Indeed, results of a retrospective analysis of patients who had received the de Gramont regimen of bimonthly 5-FU+LV led one group of investigators to suggest that suboptimal dosages were being used in some cases and to recommend that higher dosages of 5-FU should be prospectively evaluated before final decisions were made as to which regimen is to be the treatment of choice.[71] The uncertainty over starting dosages of 5-FU is currently reflected by the choice available (370–425 mg/m^2 with LV 20 mg/m^2 for 5 days every 4 weeks for six cycles) in the ongoing PETACC trial of 5-FU versus the novel TS inhibitor raltitrexed in the adjuvant treatment of patients who have undergone apparently curative surgery for colorectal cancer.[72]

Schedules of well-documented regimens are often amended to take account of toxicity or practical considerations. For example, the Mayo regimen is sometimes adjusted so that 5-FU+LV is given for three or four rather than five consecutive days to ameliorate toxicity. Furthermore, if the oncologist only attends an outpatient clinic on a weekly basis, the regimen may be adapted to a weekly schedule of 5-FU with low-dose LV (e.g. as permitted in the UK QUASAR protocol).[73] The frequency of public holidays may also result in underestimation of toxicity: where such holidays coincide with first cycles, it is possible that treatment will be given for 4 days rather than 5 days.[67]

Because colorectal cancer is so common, numerous attempts have been made to improve response rates and survival through the addition of a variety of modulating agents to 5-FU therapy. Substances other than LV that have increased the cytotoxicity of 5-FU in experimental systems include methotrexate, cisplatin, PALA, thymidine and IFN.[8] However, none have been shown in prospective randomized trials to confer benefit compared with 5-FU alone.

Novel agents and the place of 5-FU

Another factor to be considered in the debate over preferred treatments for advanced colorectal cancer is

that of development of novel therapies. In recent years, several new drugs have entered developmental phases II and III, and the introduction of novel and effective treatments to clinical practice is likely to profoundly affect clinicians' perceptions of the overall benefit to patients of 5-FU-based therapies, particularly in view of their toxicity and inconvenience.

One of these new agents, CPT-11 (irinotecan), is an inhibitor of topoisomerase I, a key enzyme in DNA replication, that has shown activity in phase II trials, with overall response rates of 15–32% in patients with previously untreated and 5-FU-resistant tumors.[74-76] Another drug of interest is oxaliplatin, a platinum compound that binds to DNA, and prevents replication and transcription. Recent phase II data have shown a response rate of 24.3% in patients who received first-line therapy with oxaliplatin.[77] An overall response rate of 10% has been reported with this agent in patients with advanced colorectal cancer refractory to 5-FU.[78] Interim results (n=200) from a randomized multicenter study in 420 patients with advanced colorectal cancer have shown an increase in overall response rate from 26 to 57% with the addition of oxaliplatin 85 mg/m^2 to the bimonthly de Gramont regimen, with corresponding progression-free survival times of 27.8 and 39.6 weeks.[79]

In addition, two published phase III studies of the quinazoline folate analog raltitrexed, given as monotherapy as a single 3-weekly 15 min infusion of 3 mg/m^2, have shown similar response rates and survival overall to the Mayo and Machover regimens of 5-FU + LV.[3,80] Raltitrexed was also associated with less stomatitis and leucopenia and more transaminase elevations than 5-FU+LV.

Conclusions

After over 40 years of clinical development, the optimum regimens of 5-FU for the management of advanced colorectal cancer remain unclear. Despite the publication of a large number of studies with a variety of schedules and modulations, and some movement on the part of the oncological community towards a preference for certain regimens over others, toxicity considerations and the failure of improvements in tumor response rates to be reflected by prolonged survival have resulted in a lack of general agreement among specialists. It also appears that, in actual clinical practice, modification of published schedules for toxicological or practical reasons is common, despite the lack of efficacy data from well-controlled studies to justify such schedule modifications. This might be considered disturbing in an era of evidence-based medicine. Furthermore, marked variations between countries in preferred regimens are apparent from discussion with colleagues and inspection of the literature (Table 4), and there is considerable variation between national cooperative groups in their routinely used comparator arms in phase III trials.

Clinical experimentation with modulated regimens of 5-FU is continuing in patients with advanced colorectal cancer. This reflects the continuation of

Table 4. 5-FU + LV regimens apparently preferred for the treatment of advanced colorectal cancer in various countries

Country	Regimen(s) and major national co-operative groups using them (where information available)
US	Roswell Park regimen of weekly 5-FU + LV (Petrelli *et al.*[27]; see Table 1)
	Mayo (NCCTG [Poon *et al.*[43]])
Canada	Mayo (NCIC)
France	De Gramont (GERCOD [de Gramont *et al.*[63]])
	Mayo
Germany	5-FU (medium dose) + LV (low dose) once weekly
	Machover
	High-dose 5-FU + LV once weekly (AIO [Köhne *et al.*[41]]; see Table 3)
Italy	Machover (GISCAD)
	Mayo
	De Gramont
Spain	Mayo
	Machover
	5-FU 48 h continuous infusion (TTD [Aranda *et al.*[31]]; see Table 3)
UK	De Gramont (MRC [Seymour *et al.*[45]])
	Mayo
	weekly 5-FU + low-dose LV

efforts to find regimens based on this important agent that will offer significant improvements in complete response rates and survival. However, exciting new possibilities are now becoming apparent through the increasing choice of novel agents that have been shown to have activity in advanced colorectal cancer. New treatments that are now appearing in the literature are of considerable interest. This is especially so where improvements in tolerability and acceptability to patients are evident, and where there is potential for novel combination therapies. Interim phase I results have indicated synergism between raltitrexed and 5-FU in patients with advanced colorectal cancer,[81] and encouraging antitumor activity of a combination of 5-FU 2400 mg/m^2 by 24 h infusion once weekly with raltitrexed 2.6 mg/m^2 every 3 weeks has recently been reported.[82] An overall response rate of 7%, with stable disease in 54% of patients, has been reported with third-line use of a 2-weekly combination of CPT-11 180 mg/m^2, 5-FU (400 mg/m^2 bolus followed by 48 h infusion of 2.4–3.0 g/m^2) and LV 400 mg/m^2 in patients with heavily pretreated advanced disease,[83] and the addition of high-dose oxaliplatin (60 mg/m^2 per week) to the Ardalan schedule of 5-FU 2600 mg/m^2 over 24 h + LV 500 mg/m^2 over 2 h[48,84] has shown activity in patients with disease progression on 5FU+LV alone.[85] It is likely that new combination therapies based on both established and novel agents, rather than continuing experimentation with 5-FU and LV, will offer the potential for future significant improvements in treatment outcomes in advanced colorectal cancer.

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