Chemotherapy of colorectal cancer liver metastases

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Introduction

Surgical removal of all known disease is the only therapy that has any major possibility to cure a patient with liver metastases from a colorectal cancer. Whether the cured fraction can be increased by additional neo-adjuvant or adjuvant chemotherapy is not known. Surgery is, however, generally not possible, and today, approximately 90% of the patients with colorectal cancer liver metastases are treated with palliative therapies.

The scientific activities during the past 10–13 years have markedly increased in advanced colorectal cancer. A considerable input of resources from academia and industry, together with a substantial improvement in the quality of clinical trials, has resulted in definite improvements for many patients during the past decade. In the absence of tumour controlling treatments, the prognosis for patients with recurrent colorectal cancer, whether to the liver alone or at other sites, is poor with, on a population level, a median survival of less than six months and a very low probability to survive beyond one or two years. Although survival in population-based materials presently is poorly known, several large international centres currently report median survivals exceeding one and a half years, indicating at least three times longer survival than a decade ago. A number of small steps have been taken, together resulting in median survival being prolonged from about 6 months to about 18 months (Table 1).

The effects of chemotherapy on objective response rates, time to disease progression, overall survival and quality of life (QoL) are well documented in advanced colorectal cancer [1,2]. Some of the gains have been shown with high statistical significance in individual trials or in meta-analyses of the trials [2–6]. Except for the trials comparing hepatic arterial infusion and systemic treatment, most trials have included patients with metastases also at other sites than the liver. However, it is reasonable to believe that the response to chemotherapy is not very dependent upon metastatic site, although the number of sites involved is important [7]. Therefore, the results of the trials are relevant also for those with liver metastases only.

Results of chemotherapy effects

Until the very end of the 1980s there was no firm evidence that treatment had any meaningful influence on the well-being of many patients. Individual patients appeared to have short-lived benefit from being treated, but the general impression was that it did not prolong survival. In 1989, two large randomised trials comparing 5-fluorouracil (5-FU) alone, the mainstay of treatment for decades, with biochemically modulated 5-FU, reported slightly prolonged survival (median about 3 months) and improved QoL by the combined regimen [8,9]. Only a few trials have been designed to allow an evaluation of whether survival is prolonged by chemotherapy. In a systematic overview [1], eleven trials, including a total of only 796 pa-

Table 1

Chemotherapy in advanced colorectal cancer

Median survival (months)	Action taken
4–5	Supportive care
5–7	Supportive care, trial patients
10–12	5-FU/leucovorin (Lv), trial patients
12–14	5-FU/Lv, good performance trial patients
14–15	5-FU/Lv + new drug, good performance trial patients
15–17	5-FU/Lv + new drug, second-line treatment
18–20	5-FU/Lv + new drug, sequential treatments, local methods

Follow-up routines are also of importance. At least 2–3 months may be explained by earlier diagnosis of metastatic disease in recent patient series compared with historical materials. Reproduced from Glimelius [12], with permission.

Table 2
Response rates and survival in randomised trials[a] or meta-analyses of the trials comparing different 5-FU-based regimens

Comparators	Ref.	No. of patients	Type of study[a]	Objective response	Time to progression	Survival	
						Median	Rel hazard
Supportive care vs. chemotherapy	[2][b]	866	M			8 vs. 12 mths***	0.65 (0.56–0.76)
	[10]	614	M				0.69 (0.60–0.81)
5-FU vs. 5-FU + leucovorin	[5]	1381	M	11% vs. 23%***		11.0 vs. 11.5 mths (ns)	
	[15]	319	C	9% vs. 22%***	3.9 vs. 6.2 mths***	10.0 vs. 12.4 mths*	
	[16]	497	C	9% vs. 21%**	4.4 vs. 6.4 mths*	12.5 vs. 13.2 mths (ns)	
5-FU vs. 5-FU + methotrexate	[4]	1178	M	10% vs. 19%***		9.1 vs. 10.7 mths*	
5-FU bolus vs. infused	[3]	1219	M	14% vs. 22%***		11.3 vs. 12.1 mths*	0.88 (0.78–0.99)
	[16]	497	C	12% vs. 21%*	4.1 vs. 6.4 mths*	12.0 vs. 13.2 mths (ns)	
	[18]	448	C	17% vs. 34%***	5.1 vs. 6.4 mths***	13 vs. 14 mths (ns)	
	[19]	306	C	19% vs. 30%**	5.5 vs. 5.8 (ns)	9.9 vs. 11.2 mths (ns)	
	[20]	149	C	18% vs. 23% (ns)		12 vs. 15 mths*	
Systemic vs. intrahepatic	[6]	291	M	14% vs. 41%***		12 vs. 16 mths (ns) (0.62–1.05)	0.81
	[44]	168	C		6.6 vs. 9.2 mths (ns)	17.6 vs. 18.7 mths (ns)	
	[45]	290	C		(ns)	13.4 vs. 14.7 mths (ns)	0.97 (0.73–1.29)
5-FU bolus vs. peroral UFT/Lv	[36]	816	C	15% vs. 12%	3.8 vs. 3.5 mths*	13.4 vs. 12.4 mths (ns)	0.93 (0.79–1.10)
	[37]	380	C	9% vs. 11%	3.3 vs. 3.4 mths (ns)	11.9 vs. 12.2 mths (ns)	
Capecitabine	[38]	602	C	15% vs. 19%	4.7 vs. 5.2 mths (ns)	13.3 vs. 12.5 mths (ns)	
	[39]	605	C	16% vs. 25%*	4.7 vs. 4.3 mths (ns)	13.3 vs. 12.5 mths (ns)	

[a] Only trials (C) reported after the meta-analyses (M) are included in the table.
[b] Includes both first-line and second-line trials, whereas the other (Ref. [10]) includes only trials in the first-line situation.
* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$
Abbreviations: mths = months; ns = non-significant; 5-FU = 5-fluorouracil; Lv = leucovorin.

tients, that tested a 5-FU-based regimen (systemic or regional administration) against a control group, where either no chemotherapy or chemotherapy was delivered late in the course, could be identified. It was concluded that chemotherapy prolonged median survival by 4–6 months. Similar conclusions were reached in two meta-analyses of the trials [2,10] (Table 2). Supportive evidence for a survival gain also comes from a trial in the second-line situation after failure on a 5-FU-containing regimen [11] (see also below).

Four of the trials randomising between chemotherapy and no/delayed chemotherapy evaluated QoL issues [1,2]. These trials and a number of trials comparing two cytostatic drug schedules have clearly shown that the QoL of individual patients can be improved by treatment. The QoL was of particular interest in several Nordic multicentre trials comparing different 5-FU-based regimens. The conclusions from these trials (see Ref. [12] for a recent review) were that improvements or prolonged stabilisation of good QoL could be achieved in about half of the patients. There was, furthermore, a clear correlation between an objective response, and improvements in QoL aspects. Also stationary disease with a duration exceeding four months was associated with a favourable QoL. A response to treatment is also a powerful and independent predictor of survival [13,14].

Biochemically modulated 5-FU

Among the numerous drugs tested for antineoplastic activity in colorectal cancer, 5-FU has been considered to be the most active agent. To exert antineoplastic activity, 5-FU has to be anabolised into active forms. Among the changes of particular im-

portance in the schedule of administration is the use of prolonged infusions. Several drugs have been employed as biochemical modulators in order to increase the therapeutic index of 5-FU [1].

The combination of methotrexate and 5-FU, generally with leucovorin rescue, has been evaluated in several randomised studies, involving altogether around 1600 patients. A meta-analysis was performed on individual data of 1178 patients included in 8 randomised trials. This meta-analysis [4] demonstrated a superiority of the combination in terms of response rate and survival (Table 2).

At least 16 randomised trials have compared 5-FU plus leucovorin with 5-FU alone. A significant advantage in terms of objective responses was observed for 5-FU plus leucovorin in 11 out of the 16 studies [1]. In six studies, a prolongation of survival for the combination regimen was reported. Ten of the studies were included in a meta-analysis [5] of 1381 patients. Again, a significant advantage of the combination therapy in terms of objective response was seen, but no difference was detected for overall survival (Table 2).

More recently, two additional large randomised trials comparing 5-FU plus leucovorin with 5-FU alone has been reported [15,16]. Both trials confirmed significantly higher response rates and prolongation of progression-free survival, whereas an overall survival gain, using modulated 5-FU, was seen in only one of the trials (Table 2).

During the past decade, chemotherapy of metastatic colorectal cancer using 5-FU has evolved along several paths; potentiation of 5-FU bolus activity by leucovorin, protracted venous infusion of low doses, infusions during one or a few days of comparatively high doses, alone or modified by leucovorin, and combinations of the alternatives. It is possible that 5-FU acts as "different drugs" depending upon schedule [17].

The conclusions to be drawn are that 5-FU modulated by either leucovorin or methotrexate results in more tumour regressions than when 5-FU is used alone. This has not been translated into considerable survival prolongation. Considering also toxicity and QoL issues, this has led to the general acceptance that modulated 5-FU is a better palliative treatment than 5-FU alone. There is at present no firm evidence showing that any of the modulated 5-FU regimens is superior to the others (Table 3). In the light of less costs, a low leucovorin dose is to be preferred for routine use since regimens using higher leucovorin doses are not superior. Simplicity also favours leucovorin in comparison with methotrexate modulation. The more recently developed "high-dose infused regimens" with modulated 5-FU are likely superior to "conventional" bolus regimens, since they result in more tumour regressions, longer times to disease progression, less toxicity and/or longer overall survival (Table 2) [16,18–20]. The comparator in those trials has been the 5-FU plus low-dose leucovorin Mayo Clinic regimen [9]. The Mayo Clinic regimen is, however, associated with a high degree of toxicity, generally considered unacceptable as a palliative treatment [21]. Other bolus regimens, like the Nordic FLv schedule, have much less toxicity. A slight increase in the 5-FU dose in Nordic FLv increased toxicity substantially without increasing anti-tumour efficacy [22].

Table 3
Palliative chemotherapy in colorectal cancer, "evidence-based" treatment options

First-line	
Bolus	Mayo
	Roswell-Park
	Machover
	Nordic FLv
Infused	AIO
	Spanish TTD
	Lokich
	Chronomodulated regimen
Hybrid	de Gramont (Lv5-FU2)
Peroral	UFT + Lv
	Capecitabine
Combinations	de Gramont + oxaliplatin
	5-FU + Lv + CPT-11
	Lokich ± Mitomycin C
Other drugs	Raltitrexed
Second-line	
Infused?	see above
CPT-11	
Oxaliplatin + 5-FU/Lv	

Reproduced from Glimelius [12], with permission. Lv, leucovorin; CPT-11, Irinotecan; UFT, tegafur and uracil.

New drugs and drug combinations

Raltitrexed (Tomudex®), a new drug causing a direct and specific thymidylate synthase inhibition without secondary effects on RNA or protein synthesis, has been compared with 5-FU plus low-dose leucovorin (Mayo Clinic regimen). Raltitrexed and 5-FU plus leucovorin had roughly the same efficacy although slightly inferior survival was noted to 5-FU plus leucovorin in one study (Table 4) [23,24]. Overall, much greater levels of toxicity (mucositis and leucopenia) were seen with Mayo Clinic regimen than with raltitrexed. In a more recently completed trial [25], raltitrexed was compared with two in-

Table 4
Results from randomised trials comparing a 5-FU-based regimen with other drugs or combinations of drugs

Comparators	Ref.	No. of patients	Objective response	Time to progression	Overall survival	Comments
5-FU/leucovorin vs. raltitrexed	[23]	439				Similar efficacy, less toxic than the Mayo schedule. Slightly inferior, more toxic than the de Gramont schedule
	[24]	459			12.7 vs. 9.7 mths**	
	[25]	905		6 vs. 5 mths*	10 vs. 10 mths (ns)	
	[26]	294		1 yr 15% vs. 8%*	1 yr 64% vs. 53% (ns)	
5-FU/leucovorin alone vs. plus oxaliplatin	[27]	420	22% vs. 51%***	6.2 vs. 9.0 mths***	14.7 vs. 16.2 mths (ns)	
	[28]	200	16% vs. 53%***	6.1 vs. 8.7 mths*	19.9 vs. 19.4 mths (ns)	Chronomodulated 5-FU
5-FU/leucovorin alone vs. plus irinotecan	[30]	102	18% vs. 40%*	5 vs. 6 mths (ns)	15 vs. 14 mths (ns)	
	[31]	387	22% vs. 35%**	4.4 vs. 6.7 mths***	14.1 vs. 17.4 mths*	de Gramont schedule
	[32]	683	21% vs. 39%***	4.3 vs. 7.0 mths**	12.6 vs. 14.8 mths*	Bolus schedule

Abbreviations and asterisk references are the same as for Table 2.

fused 5-FU-based regimens (de Gramont, Lokich). Although similar response rates and survival were seen in the three arms, time to disease progression and QoL were inferior in the raltitrexed arm. In yet another recently completed trial, raltitrexed was more toxic than two variants of the de Gramont schedule [26]. Since it also gave a shorter time to progression, this and other recent studies add to the conclusion that raltitrexed alone is an inferior treatment than an optimal 5-FU plus leucovorin regimen. It may still have a role in combination with other drugs since it is convenient to administer.

Oxaliplatin (Eloxatin®) is a third-generation platinum compound that has only a relatively low activity as a single agent. This compound has, however, yielded favourable results in association with 5-FU and leucovorin. In a randomised study, the bi-monthly schedule of leucovorin plus 5-FU (de Gramont) was designed to investigate the effect upon progression-free survival of adding oxaliplatin to this schedule [27]. Response rates and progression-free survival were significantly improved but not overall survival ($P = 0.12$) (Table 4). The addition of a flat infusion of oxaliplatin to chronomodulated 5-FU and leucovorin similarly increased response rates, but not overall survival [28].

Even if the addition of oxaliplatin to 5-FU plus leucovorin has not prolonged overall survival, either to any great extent, or statistically significantly, it has been accepted as a superior regimen to 5-FU plus leucovorin alone. Although primarily tested with the bi-monthly de Gramont schedule, including simplified variants, it has been combined also with other infused regimens, bolus 5-FU administration, per-oral fluoropyrimidines (see below), raltitrexed and irinotecan (see below).

Irinotecan, CPT-11 (Campto®) is a topoisomerase I inhibitor which, in several phase II studies, has shown activity in patients who had failed 5-FU/leucovorin treatment. The results of two randomised studies, in which CPT-11 in second-line was compared with best supportive care (BSC) and best estimated chemotherapy regimen, respectively, in patients with 5-FU refractory cancer, showed a significant benefit for CPT-11 in terms of improved survival (Table 5) [11,29]. Randomised studies have evaluated the addition of CPT-11 to infused 5-FU and leucovorin (48-h bimonthly and weekly 24 h) in first-line treatment [30–32]. In all three studies, the 5-FU/leucovorin + CPT-11 combination gave more responses than 5-FU/leucovorin alone, longer times to treatment failure and overall survival, median about two months (Table 4). In one of the trials, a CPT-11 alone arm was also included, yielding similar results to the 5-FU/leucovorin combination [32]. Just like oxaliplatin, irinotecan has also been authorised for use in first-line metastatic colorectal cancer in most countries and is regarded as a superior treatment to 5-FU plus leucovorin alone.

A combination of either oxaliplatin or irinotecan with 5-FU plus leucovorin has higher antitumour activity than 5-FU plus leucovorin alone since the number of objective responses and time to progression are prolonged. Overall survival is also slightly prolonged, albeit not statistically significantly using oxaliplatin. Differential use of second-line therapy

Table 5
Randomised trials in the second-line situation after failing 5-FU/leucovorin (+CPT-11)

Comparators	Ref.	No. of patients	Time to progression	Survival	
				Median	1 year
BSC vs. CPT-11	[11]	279		6.5 vs. 9.2 mths***	14% vs. 36%
Infused FU vs. CPT-11	[29]	256	2.9 vs. 4.2 mths*	8.5 vs. 10.8 mths*	32% vs. 45%
Infused FU vs. infused 5-FU + oxaliplatin	[40]	463	2.7 vs. 4.6 mths***		

Abbreviations and asterisk references are the same as for Table 2. BSC, best supportive care.

(see below) may explain this difference. It also appears that the superiority of any of the combinations is independent of the chosen 5-FU plus leucovorin regimen.

We presently do not have any knowledge of the best combination schedule, although many would likely consider either oxaliplatin or irinotecan with the bi-monthly de Gramont-schedule (including variants) as a preferred reference schedule. Infused schedules have been preferred by many European investigators, whereas bolus regimens have been preferred in the US. However, a large US Intergroup Study (N9741) [33], after having randomised 795 patients to either of 3 groups (the trial started with 6 groups), a bolus 5-FU plus leucovorin regimen with irinotecan (Saltz-regimen, or IFL) as the control group, an oxaliplatin/de Gramont (FOLFOX-4)-regimen and a combination of irinotecan and oxaliplatin, recently showed a response rate of 38% for the FOLFOX-4 regimen compared with 29% ($P = 0.03$) for IFL, a median time to progression of 8.8 months vs. 6.9 months ($P = 0.0009$) and an overall survival of 18.6 months vs. 14.1 months ($P = 0.002$), respectively. Irinotecan was available as second-line treatment, whereas oxaliplatin was not. Thus it is possible that the survival difference, favouring oxaliplatin as first-line treatment, can be explained by a difference in the availability of an effective second-line regimen (see also below). The irinotecan-containing bolus Saltz-regimen also turned out to be slightly too toxic, with an unacceptable number of toxic deaths [33,34]. A European randomised trial compared irinotecan with oxaliplatin, both in combination with the de Gramont-schedule. The activity in the first-line situation appeared similar between the two schedules, FOLFIRI and FOLFOX [35]. This further supports the notion given above that the survival difference in the N9741-trial can be caused by the different availability of second-line treatments between the treatment groups.

Both irinotecan and oxaliplatin add toxicity and costs to the 5-FU plus leucovorin treatment. The toxicity profiles of irinotecan (preferentially diarrhoea, some alopecia) and oxaliplatin (preferentially paresthesias) are entirely different, and it is impossible that one of the drugs can be favoured over the other. Since the overall survival gain using a combination regimen upfront, or a 5-FU plus leucovorin alone-regimen as first-line treatment with any of the newer drugs later in the course, is likely small, the regimen to choose must be evaluated individually and discussed with the patient.

Oral fluoropyrimidines

Tegafur and uracil (UFT) are composed of a 1 : 4 fixed molar ratio of Ftorafur (tegafur) and uracil. Tegafur is a fluorouracil prodrug, and uracil competes with 5-FU as a substrate for dihydropyrimidine dehydrogenase (DPD), an enzyme responsible for 5-FU catabolism. UFT may be administered orally. The efficacy and safety profile of UFT + leucovorin have been compared with 5-FU plus leucovorin as first-line chemotherapy. Peroral UFT + leucovorin gave results similar to intravenous 5-FU + leucovorin (Table 2) [36,37]. Capecitabine (Xeloda®) is another oral drug that has shown promising activity and toxicity pattern. It is converted to 5-FU, preferentially in tumour tissue, by the enzyme thymidine phosphorylase. Again, results from randomised multicentre phase III studies are similar to intravenous 5-FU + leucovorin [38,39]. Objective response rates tended, however, to be higher with capecitabine in both trials. Since the comparator to the two oral drugs was the bolus Mayo Clinic schedule, it is not known whether a more favourable toxicity profile would have been seen also in comparison with other bolus, or infused regimens. Patients prefer oral administration, but they are not willing to compromise efficacy. Other oral 5-FU prodrugs may also be able to replace 5-FU in first-line therapy, but they are unlikely to significantly improve outcomes as single agents compared with an optimal intravenous 5-FU regimen. It is possible to combine the oral drugs also with all of the newer agents, and several phase I–II trials have shown promising activities. Phase III trials are ongoing.

Second-line treatment

As described above, 5-FU-based regimens were used extensively for palliation up until about 1990, without any firm evidence of activity. After failure on one 5-FU-containing regimen, it was observed that some patients could respond to a modified 5-FU-based regimen. If the first regimen used bolus 5-FU, infused 5-FU was frequently used based upon the assumption that the anti-tumour activity was different [17]. Responses were seen, but whether this was a sufficiently effective treatment was never evaluated properly. It was not until a new drug, irinotecan, with an apparently different mode of action, appeared, that conclusive trials were performed. Irinotecan significantly prolonged survival in patients refractory to 5-FU when compared with either BSC [11] or infused 5-FU [29] (Table 5). Oxaliplatin with 5-FU plus leucovorin and raltitrexed were also used frequently in pretreated patients, without any firm evidence of activity from randomised trials. It was not until recently [40] that a large randomised trial using oxaliplatin with 5-FU plus leucovorin (FOLFOX-4 regimen) revealed superior activity to either drug alone after following an irinotecan, 5-FU plus leucovorin (IFL) regimen. About 35–40% of the patients had symptom relief, compared with 10–15% in the control arms, and median time to progression was prolonged from below 2 months to slightly more than 4 months. Objective responses were seen in about 10% of the patients treated with FOLFOX-4 compared with 0–2% of those treated with either the de Gramont schedule or oxaliplatin alone. It is too early to evaluate survival; nonetheless, it is likely that this treatment will be sufficiently effective as routine treatment. In a randomised phase II study, the activity of three schedules, either irinotecan with 5-FU plus leucovorin, oxaliplatin with 5-FU plus leucovorin or irinotecan with oxaliplatin appeared similar in patients failing a 5-FU-based regimen [41].

Remaining issues and concluding remarks

In spite of the progress seen, several issues, not specifically dealt with in this review, remain. One of them is when to start treatment in patients without tumour-related symptoms, another when to stop treatment in cases of a response. Many would argue that the Nordic trial in asymptomatic patients gave a conclusive result, namely to start to treat once metastatic disease is diagnosed [42]. The trial randomised patients to immediate chemotherapy, or to chemotherapy delayed until the patient had become symptomatic. Symptom-free and overall survival and QoL were significantly better in patients randomised to primary chemotherapy. Unless you are interested in getting as long survival as possible in your patient material, it may well be that many patients would do better to wait until signs of disease progression are seen. Postponing treatment until symptoms appear may, however, be too late in some patients, compromising overall survival (median 5 months difference in the Nordic trial) [42].

A Medical Research Council (MRC Cr06b) trial randomised patients who had a response or disease stabilisation after 3 months of therapy to continued treatment or a break, with reinstitution of treatment when progressive [43]. The trial noticed that some QoL-aspects were better if treatment was interrupted, and survival was not compromised. These results challenge present routines at many centres, although they cannot yet be considered conclusive. In the trial, only single-agent therapy (5-FU with leucovorin or raltitrexed) was used. Whether the results are true also for more effective combination therapy is thus not known, although this may well be the case. Slightly fewer patients than aimed at were also included, thus reducing statistical power.

Other remaining issues concern the role of regionally administered chemotherapy [6] in the era of improved systemic treatments. This approach, together with chronomodulated administration, is possibly the one that results in the highest remission rates, but both methods have inconveniencies compared with regular systemic administration. In the meta-analysis of trials comparing intrahepatic arterial chemotherapy with systemic 5-FU, more responses were seen in the patients allocated to regional therapy than for those allocated to systemic treatment (Table 2). There was no significant difference in overall survival. When intrahepatic chemotherapy was compared with an adequate 5-FU-based regimen, given systemically, no benefit was, however, seen [44,45]. Thus, even if this approach has been popular at some centres for many years, its use remains experimental. If in an individual patient it remains important to cause maximum down-sizing, it may be important in addition to adequate systemic combination chemotherapy.

The results of chemotherapy have improved substantially during the past 15 years. From being a treatment of unproven value, benefiting very few, during the 1980s, it is now a well-documented treatment-prolonging survival, relieving or postponing symptoms in many, and potentially curing a few if combined with local methods, particularly surgery. Median survival has been prolonged from less than

6 months to above 18 months in many patient series (Table 1). Earlier detection of metastatic disease, generally because of routinely performed imaging with methods like spiral-CT (computerised tomography) and MRI (magnetic resonance imaging), detecting smaller lesions than possible before, is responsible for some of the much longer survival presently seen. The extra months, or years, gained are generally good months in spite of the toxicity seen. Future improvements are probable using a multidisciplinary approach, together with a hope that new treatments, based upon recent tumour-biological knowledge, will eventually yield clinically meaningful effects.

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