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Systemic Treatment of Colorectal Cancer

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INTRODUCTION

COLORECTAL CANCER (CRC) is among the most common cancer types, second to breast cancer in women and third to lung cancer and prostate cancer in men. The prognosis depends largely on the extent of disease at the time of diagnosis, i.e. stage according to Dukes or the TNM system, although several other factors have been found to independently influence prognosis [1]. At present, less than 50% of all CRC patients are cured of this disease. Despite long-standing efforts for early diagnosis in order to improve the cure rate, there is still no established screening procedure which is widely practised.

This paper deals with the systemic treatment of CRC both in metastatic disease and in the adjuvant setting. Since locoregional treatment to the liver via the hepatic artery is not strictly systemic treatment, the reader is referred to two recent reviews of the subject, one arguing in favour and one against an established benefit [2, 3].

Metastatic disease

Almost by definition, metastatic CRC is incurable. There are, however, a few exceptions to this. Long-term disease-free survival (or cure) can be achieved in patients undergoing surgical resection of lung or liver metastases, provided this is the only metastatic site. There are rare reports of apparent cures by chemotherapy which may be overlooked in large studies by early reporting of results [4]. However, the use of chemotherapy in CRC is aimed at palliation and prolongation of survival. Endpoints for studies have been response, survival time, improvement of symptoms and symptom-free survival time.

The characteristics of patients treated in a specific study is very important. Their influence on survival is higher than any treatment. Selecting patients with good prognostic factors is likely to achieve longer survival times even without any treatment. Prognostic factors for survival are shown in Table 1 [5, 6]. Likewise, response to chemotherapy depends on the patients condition and other variables, though the predictibility is not that good. Factors reported to influence chemotherapy response are shown in Table 2 [6, 7].

5-Fluorouracil single agent treatment

5-Fluorouracil (5-FU) has been the most widely used and studied drug in CRC. Early on in its use in CRC, it was found to be effective. However, the methods then used to document efficacy and measure disease parameters were not as well

Table 1. *Metastatic colorectal cancer: prognostic factors for survival* [5, 6]

Performance status
Grade of anaplasia
Measurable disease*
Symptoms*
Elevated LDH and/or CEA and/or WBC
Lung versus liver metastases

* Presence indicates poor prognosis. LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; WBC, white blood cells.

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Table 2. Metastatic colorectal cancer: prognostic factors for response to chemotherapy [6, 7]

Performance status
LDH
WBC

Table 3. Factors responsible for the variability of response to 5-FU (and other agents) in CRC

Patient selection prior to randomisation
Treatment early or late during the course
Evaluability of a given study
Method, frequency and quality of tumour measurements
Extramural review of responses
Drug dose intensity

developed, and are by no means comparable to our present standards. For example, palpable liver size and scinti scans of the liver were used to follow the size of liver metastases. These methods are likely to have under- or overestimated the effects of treatment. Furthermore, due to the lack of effective imaging procedures, patients were treated when the disease was much more advanced than is the case now.

The response rate to 5-FU single-agent treatment has been estimated to be around 20% from older studies, many of whom were uncontrolled. Due to the numerous phase III trials performed in the 1980s comparing 5-FU with 5-FU plus folinic acid (FA) or sequential methotrexate and 5-FU, we are fortunate to have reliable results on the effect of 5-FU alone in CRC. But still the response rate varies between 3 and around 20%. The reasons likely to be responsible for this variability are listed in Table 3.

There is no doubt about a dose–response relationship for 5-FU in CRC. This has been shown by Ansfield [8], confirmed by Hryniuk [9] and again by ourselves [10] for the newer studies. However, there is a similarly clear dose–toxicity relationship which limits the use of higher 5-FU doses for most patients. Whenever response data are compared, one has to look for toxicity data as well, and try to make conclusions by looking at equitoxic regimens.

Which is the best way to give 5-FU in CRC? To answer this question, there is not a lot of data from randomised studies available. 5-FU can be given by bolus injection or by infusion over hours, days or weeks. Bolus injections or short infusions are repeated 5 times daily every 3 to 5 weeks or weekly. When 5-FU is given by infusion, higher doses (50–200%) can be safely given. This, however, does not mean higher exposure of tumour cells to active metabolites. The amount of 5-FU anabolised to the active metabolites FdUMP and FUTP depends on the amount catabolised to inactive metabolites. The enzyme responsible for the latter pathway is saturated when 5-FU is given by bolus or short-term infusion. With longer infusions, more 5-FU is broken down which allows more of the drug to be given without necessarily achieving better responses. However, longer infusions of 5-FU cause a somewhat different toxicity profile (more frequent diarrhoea, skin toxicity), indicating different sensitivities of varying tissues. Weekly bolus injections have the advantage of easy application and easy management of toxicities. Depending on the condition of the patient, the starting dose should be 600–800 mg/m^2/week. This can then be tailored to the individual patients tolerance of accepting mild to moderate toxicity. If grade III or IV toxicity occurs, one injection can be omitted and the next dose reduced by 25%. Treatment effects can be evaluated after 6 to 8 weeks. If by then no improvement is evident, continuation is not likely to have a significant impact on the course of disease. Alternatively, 5-FU can be given daily for 5 days at a bolus dose of 450 mg/m^2/day repeated every 3 to 4 weeks. The disadvantage of this regimen is that dose modifications are only possible for the next cycle and not weekly.

Infusional 5-FU. After it was shown that 5-FU can be continuously infused over weeks at dosages of 300 mg/m^2/day [11], several randomised studies were performed (Table 4) [12–14]. They confirmed a higher response for infusional 5-FU, but no significant effect on survival. At present, infusional 5-FU does not seem to be accepted as a standard treatment especially because of its more difficult application. However, it may prove to be advantageous in situations where a higher response rate is important, e.g. the preoperative or neoadjuvant setting. Also, in the adjuvant treatment of rectal cancer in combination with radiotherapy, infusional 5-FU has been found to be superior to bolus 5-FU [15].

Very high doses of 5-FU (2.6 g/m^2) can be given weekly by a 24-h infusion, even with the addition of biochemical modulators

Table 4. Continuous infusion versus bolus injection of 5-FU in CRC. Results of randomised studies

	Lokich [12]		Hansen [13]		Weinermann [14]	
	Infusion	Bolus	Infusion	Bolus	Infusion	Bolus
n	87	87	~150	~150	88	86
Schedule	300 mg/m^2/day continuous	500 mg/m^2/day ×5 every 5 weeks	300 mg/m^2/day continuous	500 mg/m^2/day ×5 then 600 mg/m^2/week	350 mg/m^2/day ×14 every 28 days	400–450 mg/m^2/day ×5 every 28 days
Response rate (CR + PR)	30%	7%	27%	19%	12.5%	7.3%
Median time to progression (months)	—	—	—	—	3.8	2.3
Median survival time (months)	10	11	13	10.6	~8.5	~8

[16]. So far, the relative effectiveness of this approach is unknown.

A further refinement of infusional 5-FU has been attempted by a French group [17]. They applied 5-FU, folinic acid and oxaliplatin via an ambulatory programmable-in-time pump that allowed infusion of varying drug dosages over time according to circadian rhythms. Although about half of the 93 patients had been treated previously, 54 (58%) achieved an objective response. These results, if confirmed, would be a major step forward.

Combination of 5-FU with other cytotoxic drugs

In addition to 5-FU, there are only a few other drugs that are able to achieve antitumoural effects in around 10% of patients with CRC, namely the nitrosoureas and mitomycin-C. Attempts to combine these drugs with 5-FU have failed to consistently improve treatment results, largely because of dose reductions needed to prevent additive toxicities.

Biochemical modulation of 5-FU

In the 1970s, laboratory methods became available for the study of 5-FU and its biochemical pathways. This gave new insights into its mechanisms of action, and opened up ways to its biochemical modulation. The mechanisms of interaction have been described in detail elsewhere [18]. While *in vitro* biochemical modulation of 5-FU can be achieved with a variety of substances, clinical studies have been largely restricted to allopurinol, methotrexate, folinic acid and PALA [*N*-(phosphonacetyl)-L-aspartate]. During the last decade, oncologists all over the world were eager to explore different methods of biochemical modulation. Although allopurinol allows an increase of 5-FU dose by a factor of about two, it has been abandoned as a modulator because of its central nervous system (CNS) toxicity and failure to improve treatment results. However, it should be kept in mind that allopurinol, when used with conventional 5-FU-dose, impairs the action of 5-FU.

Methotrexate (MTX) is a potent modulator of 5-FU in *in vitro* and *in vivo* systems. The results of phase III studies in CRC comparing sequential application of MTX and 5-FU are conflicting. A recently published German trial utilising high dose intensity 5-FU in the control arm failed to identify a significant difference in response and survival [4]. Previously, the Piedmont Oncology Group has demonstrated a significant survival advantage for patients treated with a 24-h as compared with a 1-h time interval between MTX and 5-FU [19]. The most important results of these phase III trials have recently been summarised [20]. A meta-analysis of all available phase III studies of sequential MTX and 5-FU versus 5-FU alone has found a significantly higher response rate for MTX/5-FU and a small, but also significant survival advantage [21].

FA (leucovorin) has been most extensively studied as a modulator of 5-FU. In previously untreated patients with metastatic CRC, various schedules of FA and 5-FU have yielded response rates between 15 and 45%, on average, markedly higher than rates expected from single-agent 5-FU. There are now final results available from several larger randomised studies comparing FA and 5-FU with 5-FU alone. Most of these studies indeed confirm the superiority of FA plus 5-FU over 5-FU alone in terms of response. In only a few, this is translated to a superiority in survival. Actually, for one study claiming a significant survival advantage, this claim was withdrawn after a longer follow-up [22].

Recently, a meta-analysis including most reported studies has been published [23]. It concludes that overall survival is not improved by the use of FA and 5-FU compared with 5-FU alone. While overall responses are more frequent with FA plus 5-FU, this advantage is lost for studies that used a high dose intensity of 5-FU in their control arm [24]. This again points to the importance of dose intensity with the use of 5-FU, and to the need of aiming at an equitoxic dose in a control group. It seems that some of the trials were initiated with the intent to demonstrate the biochemical modulation of 5-FU by FA, which they clearly did, rather than to show an increase in therapeutic index. After all these studies, the oncology community is not unanimous about the use of FA and 5-FU. While some are claiming FA and 5-FU to be the new standard, others tend to be less convinced.

Undoubtedly, the best results in terms of response, quality of life and survival have been reported by the North Central Cancer Treatment Group (NCCTG) [5]. Their regimen (Table 5) is easy to manage and not too expensive with the use of low dose FA.

Very favourable results were reported in 1989 with the combination of α-interferon and 5-FU, claiming 13 objective responses in 17 previously untreated patients with metastatic CRC [25]. In the meantime, results of two phase III studies have been reported which essentially showed no advantage of this combination when compared with other currently used chemotherapy regimens. One study compared the combination of α-interferon and 5-FU with 5-FU alone, and achieved response rates of 25 and 20%, respectively, with no difference in median overall survival, but higher toxicity in the combination regimen [26]. The other study compared the combination of α-interferon and 5-FU and 5-FU plus leucovorin [27]. They achieved response rates of 21 and 19%, respectively, with an identical overall survival. Following these studies, the combination of α-interferon and 5-FU does not seem to be an alternative to single-agent 5-FU or 5-FU and folinic acid.

New drugs

CRC is one of the entities included early in the phase II evaluation of new drugs. Unfortunately, no new active drugs have been established so far. Several new agents are currently undergoing clinical evaluation. CPT-11, a camptothecin derivative, has achieved a partial response in 17 of 63 (27%) patients, many of whom had been treated previously [28]. More studies of this and other topoisomerase I inhibitors are now ongoing.

Immunotherapy

Although several avenues are presently being explored, there is as yet no active immunotherapy for the treatment of metastatic or recurrent CRC. Based on observations in clinical models, several immunological approaches are likely to work in the presence of minimal disease only, i.e. in the adjuvant setting. Results of two approaches have now been reported. Hoover and colleagues reported the use of active specific immunotherapy with autologous tumour cells admixed with BCG, and achieved a significant survival advantage in the adjuvant treatment of colon cancer [29]. Riethmüller and colleagues used the mono-

Table 5. Regimen of FA plus 5-FU for the treatment of metastastic colorectal cancer [5]

FA	20 mg/m²/day i.v. bolus injection, 10 min later followed by:
5-FU	425 mg/m²/day i.v. bolus injection, given on 5 consecutive days, repeated from day 29 to day 33.

clonal antibody 17-1 A in Dukes C disease, and saw a significant reduction in distant relapse and survival benefit [30]. However, these results will have to be confirmed by others. New immunotherapy trials will be aimed at the induction of an immune response through autologous or allogeneic cells transfected with cytokine genes, and at the induction of response to tumour-specific proteins, e.g. *ras*, p53.

Preoperative chemotherapy

Preoperative chemotherapy aims at a decrease of the primary tumour and increase in resectability rate. In colon cancer, this approach has not yet been studied since the extent of the primary can not reliably be determined preoperatively, and the efficacy of the present systemic treatment is too poor. In rectal cancer, however, tumours can be classified as unresectable or marginally resectable by computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or endosonography. In addition, the combination of chemotherapy and radiotherapy has been shown to be effective in patients with locally recurrent disease [31]. In a study using preoperative chemo/radiotherapy in unresectable or locally advanced rectal cancer, this approach was shown to be feasible and achieved resectability in 100% of patients [32, 33]. Surgical morbidity is not adversely affected [34]. It is too early to determine the impact on distant relapse and on survival.

Adjuvant chemotherapy

Adjuvant treatment of colorectal cancer is a very good example, where persistence and consequence in the design and execution of clinical trials have eventually succeeded in the establishment of a new standard. Unlike treatment of metastatic disease, colon cancer and rectal cancer are dealt with separately.

Colon cancer. The use of adjuvant chemotherapy in colon cancer has been mainly restricted to those Dukes stages (B2, C) which have a >50% risk of recurrence. As in metastatic disease, 5-FU has been the mainstay of treatment. In the 1960s and 1970s several studies were reported which compared 5-FU alone with an untreated control. None of these trials convincingly proved an advantage for 5-FU-treated patients. When the addition of methyl-CCNU [1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea] with or without vincristine was claimed to improve response rates in metastatic disease, several studies tested this combination in the adjuvant setting. One of these trials reported a small survival benefit [35], which would seem to have lost its significance with longer follow-up. In two prospectively randomised studies, the antihelmintic agent levamisol was found to be ineffective compared to placebo in the adjuvant treatment of colon cancer [36, 37]. Only a matched case study reported a beneficial effect of levamisol in 1978 [38]. These data prompted the NCCTG to inititate a study with a combination of 5-FU and levamisol [39]. When an interim analysis suggested a significant effect, an Intergroup study was initiated in 1984. The results of this study, which compared 5-FU plus levamisol with levamisol alone and an untreated control group, were reported in 1990 and have recently been updated [40]. They conclusively demonstrate a highly significant improvement in recurrence rates and death rate with the use of 5-FU plus levamisol as compared to the untreated control in Dukes C disease. Because neither the NCCTG nor the Intergroup study used 5-FU alone, the exact role of levamisol and its impact on the observed treatment effects are not known. While the ineffectiveness of 5-FU in the earlier trials is considered to be sufficient proof by some, careful analysis of the older adjuvant trials suggests that, for several reasons, 5-FU may not have been adequately tested in this setting (Table 6). For example, the intended dose intensity for 5-FU ranged from 4.9 to about 26 g/m^2/year as compared to 23.85 g/m^2 in the Intergroup study. The only study that showed significant improvement in disease-free survival is the one intending to use 26 g/m^2/year [41]. Also, the Veterans Administration Surgical Oncology Group (VASOG) study [42] showed a significant survival advantage for Dukes stage C patients receiving 5-FU plus methyl-CCNU as compared to an untreated control. Since in this study, the given dose intensity of 5-FU was low (8.9 g/m^2/year) and the contribution of methyl-CCNU is questionable, it could be argued that 5-FU as a single agent given at sufficiently high doses (>23 g/m^2/year) could be effective in the adjuvant treatment of colon cancer.

Several issues are currently being studied in a number of randomised trials. The combination of 5-FU plus FA has already been shown to be superior to a no treatment control [43]. Several trials are comparing 5-FU plus folinic acid plus/minus levamisole in varying schedules with 5-FU plus levamisole. The EORTC has included the intraportal treatment approach in their design. The Swiss group is the only one testing a higher dose of single-agent 5-FU (600 mg/m^2/week). The NCCTG has completed accrual to a study comparing 12 months with 6 months of 5-FU plus levamisole, and these results will come out shortly.

For Dukes stage B2, equivalent to TNM stages T3 N0 M0 and T4 N0 M0, a benefit of adjuvant chemotherapy has not been confirmed conclusively. It is possible that a significant effect will only be detected in patients with additional risk factors, e.g. invasion of adjacent organs or perforation (T4) and/or unfavourable cellular kinetic patterns [44]. It is also desirable to study other potential risk factors, e.g. genetic alterations, expression of adhesion molecules and growth factors or growth factor receptors, activity of thymidylate synthase, to eventually be able to define subgroups of patients most likely to benefit from adjuvant treatment.

Side-effects of 5-FU and levamisole include mainly mucositis, diarrhoea and bone marrow depression. In a few patients, multifocal leucoencephalopathy may be detected on MRI following the development of CNS symptoms [45]. In the Intergroup study, 30% of patients have prematurely discontinued their treatment after a median of 5 months [46].

Rectal cancer. Several randomised trials have shown a significant benefit of combined chemotherapy and radiotherapy for patients with Dukes B, B2 or C rectal cancer (for a detailed review, see [47]). Most of these studies utilised a combination of 5-FU and methyl-CCNU. After it became apparent that methyl-CCNU was leukaemogenic [48], two studies, one by the Gastrointestinal Tumor Study Group and one Intergroup study, have demonstrated that methyl-CCNU could be eliminated from the treatment [49, 50]. Following a consensus development conference, the US National Cancer Institute has published

Table 6. Reasons why 5-FU as single agent may have been ineffective in the adjuvant treatment of colon cancer

Patient selection (unavailability of techniques to rule out metastastic disease)
Low dose intensity
Duration of treatment
Low number of patients
Inclusion of both colon and rectal cancer

recommendations for patients with Dukes B2 or 3 or Dukes C rectal cancer who will not be treated on a study [51]. Details of these recommendations are given in Table 7.

In the meantime, the NCCTG has reported a further improvement of treatment by the use of continuous intravenous infusion of 5-FU during the time of radiation therapy [15]. Although the reported differences in relapse-free and overall survival are significant, final conclusions and recommendations must await detailed publication. If a beneficial effect of infusional 5-FU is confirmed regarding development of distal metastases, this method of 5-FU application may be a new candidate for adjuvant trials in colon cancer as well.

Despite the advances in adjuvant chemotherapy of CRC, surgery remains the most important part of curative treatment. The quality of surgical therapy cannot be substituted by chemotherapy and it must not be compromised.

Questions of practical interest

Is any chemotherapy superior to best supportive care? In two consecutive studies performed by the VASAG from 1965 to 1973, treatment with 5-FU was associated with longer survival compared to no treatment in patients with residual disease following surgery [52]. A recently published Austrian study tested combination chemotherapy with 5-FU, FA and cisplatinum against supportive care alone [53]. Despite small numbers, they found a statistically significant survival benefit for patients having received chemotherapy accompained by better quality of life scores. Thus, it is highly likely that, in defined groups of patients, chemotherapy is better than supportive care alone. This statement is supported by the results of the Scandinavian group [54]. There are, however, patients with far advanced disease who are unlikely to benefit from chemotherapy. These patients are usually not included in clinical trials. Therefore, it is difficult to define this subgroup. However, patients with poor performance status (WHO 3 or 4) or massive tumour load should probably not receive chemotherapy.

Is there any indication for second-line chemotherapy? Most patients who are primarily or secondarily unresponsive to chemotherapy are highly unlikely to respond to any other systemic treatment. These patients are usually not eligible for phase II drugs, though if in a good general condition, they may be candidates for phase I studies.

When should chemotherapy be initiated? In the past, many physicians have been reluctant to treat asymptomatic patients since some remain asymptomatic for months. Recently, the Nordic Gastrointestinal Tumor Adjuvant Therapy Group has shown that early chemotherapy in these patients is significantly superior in terms of survival, duration of asymptomatic period and the time to disease progression by about 6 months over primary expectancy [54].

Is serum carcinoembryonic antigen (CEA) a reliable parameter for response to chemotherapy? Sufficiently exact and reproducible measurement of metastases requires CT scanning in most patients. Thus, it would be preferable to have a serum marker which is less expensive and more easily determined. Unfortunately, during the first 4–6 weeks of treatment when it would be rather important to detect non-responding patients, CEA may sharply increase in responding patients probably due to tumour destruction [55]. Later in the course of treatment, serial CEA levels have a higher predictive value [56].

How should patients who relapse following adjuvant chemotherapy be treated? No data are available for this population at the present time. Theoretically, the longer the disease-free interval the more likely that the response to chemotherapy in these patients will become similar to chemotherapy-naive patients.

Should patients receive adjuvant treatment outside of clinical trials? Those patients with advanced age and concomitant morbidity who are unlikely to tolerate the presently recommended treatments or who are not likely to be compliant should not be treated. All others should be informed about the possible benefits and the risks in order for them to be able to participate in the decision making. Preferably, however, at this stage of the development, patients should be entered into clinical trials.

Table 7. Recommendations of the US National Cancer Institute for the adjuvant therapy of rectal cancer Stages Dukes B 2, 3 or Dukes C [51]

Week 1 + 5	5-FU 500 mg/m²/day for 5 days
Week 9	Radiation therapy to tumour area and regional lymph nodes, 45 Gy over 4 to 6 weeks followed by 5, 4 Gy boosts in three fractions to the tumour bed Give 5-FU 500 mg/m²/day for 3 days during the first and last week of irradiation
4 + 8 weeks after radiation	5-FU 450 mg/m²/day for 5 days

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