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Systemic Treatment of Colorectal Cancer

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INTRODUCTION

COLORECTAL CANCER (CRC) is one of the most common cancer types, second to breast cancer in women and third to lung and prostate cancer in men. The prognosis depends largely on the extent of disease at the time of diagnosis, i.e. stage according to Duke's or the TNM-system, although several other factors have been found to independently influence prognosis. To date, less than 50% of all CRC patients are cured of the 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 or the portal vein is not strictly systemic treatment the reader is referred to a recent review on this specific subject by Patt *et al.* [1].

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 [2]. However the use of chemotherapy in CRC is aimed at palliation and prolongation of survival. Endpoints for studies have been response, survival time and improvement of symptoms.

The characteristics of patients treated in a specific study is very important. Its influence on survival is higher than any treatment. Selecting patients with good prognostic factors is likely to achieve long survival even without any treatment. Prognostic factors for survival are shown in Table 1. Likewise, response to chemotherapy depends on the patients condition and other variables, though the predictability is not that good.

Table 1. Metastatic colorectal cancer: prognostic factors for survival [3, 4]

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

*Presence indicates poor prognosis.
LDH = lactate dehydrogenase; CEA = carcinoembryonic antigen; WBC = white blood cell count.

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Table 2. Metastatic colorectal cancer: prognostic factors for response to chemotherapy [4, 5]

Performance status
Lactate dehydrogenase
White blood cell count

Factors reported to influence chemotherapy response are shown in Table 2.

5-FLUOROURACIL SINGLE AGENT TREATMENT

5-Fluorouracil (5-FU) has been the most widely used and studied drug in CRC. Early on, during its use in CRC, it has been found to be effective. However, the methods to document efficacy and measure disease parameters were not developed as well and are by no means comparable to our present standards. For example, palpable liver size and scinti scans of the liver have been used to follow the size of liver metastases. These methods are likely to have under- or overestimated the effect 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 which were uncontrolled. Due to the numerous phase-III trials performed in the 1980s comparing 5-FU with folinic acid (FA) plus 5-FU 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 [6], confirmed by Hryniuk [7] and again by ourselves [8] for the newer studies. However, there is a similarly clear dose–toxicity relationship which limits the use of higher 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 3–5 weeks or weekly. When 5-FU is given by infusion, higher doses (50–200%) can be given safely. 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 to give more drug without necessarily achieving better responses. Longer infusions of 5-FU, however, 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 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 6–8 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 3–4 weeks. The disadvantage of this regimen being that dose modifications are only possible for the next cycle and not weekly as in the weekly regimen.

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

Combination of 5-FU with other cytotoxic drugs

In addition to 5-FU there are only very few drugs, that are able to achieve antitumour 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 ways to its biochemical modulation. The mechanisms of interaction have been described in detail elsewhere [9]. 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. During the past decade oncologists all over the world have explored different modes of biochemical modulation. Although it allows the increase of 5-FU dose by a factor of about two, allopurinol has been abandoned as a modulator due to its CNS-toxicity and failure to improve treatment results. It should, however, be kept in mind, that allopurinol, when used with conventional FU dose, impairs the action of 5-FU.

Methotrexate (MTX) is a potent modulator of FU *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 a high dose intensity of 5-FU in the control arm failed to identify a significant difference in response and survival [2]. Previously the Piedmont Oncology Group has demonstrated a significant survival advantage for patients treated with a 24 h as compared with a 1 h interval between MTX and 5-FU [10]. The most important results of these phase-III trials have recently been summarised [11].

Folinic acid (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 the average markedly higher than what is to be expected from single agent 5-FU.

There are now final results from several larger randomised studies comparing FA and 5-FU vs. 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 few, this is translated to a superiority in survival. Actually, for one study claiming a significant survival advantage this claim has been withdrawn after a longer follow-up [12].

Recently a meta-analysis including most reported studies has been published [13]. 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 [14]. 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) [3]. Their regimen (Table 4) is easy to manage and not too expensive with the use of low dose FA.

QUESTIONS OF PRACTICAL INTEREST

Is any chemotherapy superior to best supportive care?

There are no recent studies which would help to answer this question. However, in two consecutive studies performed by the Veterans Administration Surgical Adjuvant Group from 1965 to 1973 treatment with 5-FU was associated with longer survival compared to no treatment in patients with residual disease following surgery [15].

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, however, 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 [16].

How should patients who relapse following adjuvant chemotherapy be treated?

No data is 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.

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 Duke's stages (B2, C) which have a >50% risk of recurrence. As in metastatic disease 5-FU has been the main stay of treatment. In the 1960s and 1970s several studies were reported which had 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 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 [17], 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 with a placebo in the adjuvant treatment of colon cancer [18, 19]. Only a matched case study reported a beneficial effect of levamisol in 1978 [20]. These data prompted the NCCTG to initiate a study with a combination of 5-FU and levamisol [21]. 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, have been reported in 1990 and recently been updated [22]. They conclusively demonstrate highly significant improvement of recurrence rates and death rate with the use of 5-FU plus levamisol as compared to the untreated control. 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 5). 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 [23]. Also, the VASOG study [24] showed a significant survival advantage for stage

Table 4. Regimen of FA plus 5-FU for the treatment of metastatic colorectal cancer [3]

FA	20 mg/m^2/day intravenous bolus injection,
	10 minutes later followed by:
5-FU	425/m^2/day intravenous bolus injection.
Given on 5 consecutive days, repeated from day 29 to day 33.	

Table 5. 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 metastatic disease)
Low dose intensity
Duration of treatment
Low number of patients
Inclusion of both colon and rectal cancer

Table 6. Recommendations of the US National Cancer Institute for the adjuvant therapy of rectal cancer Stages Duke's B2, 3 or Duke's C

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 4–6 weeks followed by 5,4 Gy boost 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.

Duke's C patients receiving 5-FU plus methyl-CCNU as compared with an untreated control. Since in this study the given dose intensity of 5-FU was low (8.9 g/m²/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/m²/year) could be effective in the adjuvant treatment of colon cancer.

Rectal cancer

Several randomised trials have shown a significant benefit of combined chemotherapy and radiotherapy for patients with Duke's B, B2 or C rectal cancer (for a detailed review, see [25]). Most of these studies utilised a combination of 5-FU and methyl-CCNU. After it became apparent, that methyl-CCNU was leukaemogenic [26], two studies, one by the Gastrointestinal Tumor Study Group and one intergroup Study, have demonstrated that methyl-CCNU could be eliminated from the treatment [27, 28]. Following a consensus development conference the US National Cancer Institute has published recommendations for patients with Duke's B2 or 3 or Duke's C rectal cancer who will not be treated on a study [29]. Details of these recommendations are given in Table 6.

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