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Feature Articles

Adjuvant and Palliative Treatments of Colon Cancer

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INTRODUCTION

COLON CANCER is one of the most common malignant diseases encountered in European countries. It accounts for approximately 10% of deaths from cancer in males and females. Although generally resectable at the time of initial diagnosis, colon cancer will relapse in 30–80% of patients, depending on the tumour extension. The 5-year survival of patients with Dukes-B and Dukes-C tumours is, respectively 60% and 30% approximately. The vast majority of surgical failures is either due to local recurrence, or abdominal extension, particularly in the liver. With these characteristics, colon cancer is one of the tumours which would most frequently be treated by chemotherapy, either as an adjuvant to surgery, or in advanced stages. Unfortunately, colon cancer and rectal cancer are resistant to the majority of chemotherapeutic agents. The only drugs with reproducible antitumour activity for colon cancer are fluoropyrimidine, particularly 5-fluorouracil (5-FU).

5-FLUOROURACIL

The first report on antitumour activity with 5-FU and other fluoropyrimidines appeared in 1957 [1]. Since then, a large variety of treatment schedules has been proposed, either by rapid intravenous injections, or by continuous intravenous infusions of short or long duration. Oral 5-FU treatment has also been proposed, but with poor results. Table 1 summarises the most commonly used treatment schedules. A particular characteristic of 5-FU treatment is that the maximum tolerated dose and the pattern of toxicity are highly schedule dependant. A 15 mg/kg daily dose is tolerable for 5 days, if given by rapid intravenous injection, but may be maintained for as long as 40 days or more when given by continuous intravenous infusion. Myelosuppression is the dose limiting toxicity for bolus intravenous injection, whereas gastrointestinal mucositis and hand–foot syndrome are generally dose limiting for continuous intravenous infusion. Although not yet completely proven, the advantage of prolonged, continuous intravenous infusion in terms of tumour response seems to be accepted, not only experimentally, but also under clinical conditions [7]. Recent results suggest that continuous intravenous 5-FU treatment produces a response rate around 30%.

The mechanism of action of 5-FU is well known. 5-FU is a prodrug which is transformed along three different pathways, to produce cytotoxic metabolites. The most important is FdUMP (fluoro-deoxy-uridine-monophosphate). FdUMP forms a ternary complex with a reduced folate and thymidylate synthetase, so that the *de novo* synthesis of thymidine is blocked. The second pathway incorporates fraudulous FU metabolites into RNA. Accessorily, fluorinated DNA is possibly also produced. The complexity of this metabolism allows for various modulations, increasing or decreasing the cytotoxic effect of 5-FU. Table 2 summarises the modulating agents which have been studied in cancer patients. The majority of them are still under investigation. Of particular interest is high dose uridine, which could possibly reduce the toxicity to normal tissues in a proportion greater than the antitumour effects [8].

5-FU COMBINATIONS

A great number of clinical studies have evaluated the antitumour activity of a combination of 5-FU and leucovorin. An overall analysis of the results, particularly those of the strictly randomised trials, indicate that the adjunction of leucovorin increases the objective response of colon cancer. However, the best combination schedule is far from being defined. A limited number of studies have compared low dose and high dose leucovorin. Contrary to what would have been expected, based on pharmacological speculations, low dose leucovorin seems to be equivalent to high dose leucovorin, as shown in Table 3.

The combination of 5-FU and interferon-alfa has been investigated in four studies, using a 5-day continuous intravenous

Table 1. Current treatment schedules for 5-FU

Reference	Schedule	
2	Rapid intravenous injection	15 mg/kg/day for 5 days, + 7.5 mg/kg every other day
3	Continuous intravenous infusion	15 mg/kg/day for 30 days or longer
4	Continuous infusion	30 mg/kg/days for 5 days
5	Rapid intravenous injection	15 to 20 mg/kg/week
6	Continuous intravenous infusion	300 mg/m^2/day for 30–180 days (median 45 days)

Table 2. Modulating agents

Agents modulating 5-FU cytotoxicity	
Leucovorin	Stabilises ternary complex
Methotrexate	Increases availability of PRPP
Phosphonacetyl-L-aspartate	Inhibits pyrimidine synthesis
High dose thymidine	Competes on catabolic pathway
Dipyridamole	Inhibits thymidine salvage
Cisplatin	Expands intracellular FH4 pool
Interferons	Unknown
Agents protecting against 5-FU cytotoxicity	
Allopurinol	Inhibits OPR-transferase
High dose uridine	Competes for RNA incorporation

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Table 3. 5-FU + leucovorin low versus high dose in advanced colorectal cancer

5-FU (mg/m²)	Leucovorin (mg/m³)	No. of patients	Response (%)	Reference
600 per week × 6	500 per week × 6	109	30.3	9
600 per week × 6	25 per week × 6	112	18.8	
500 per day × 5 every 4 weeks	—	107	12.1	
370 per day × 5	200 per day × 5	35	25.7	10
370 per day × 5	20 per day × 5	37	43.2	
500 per day × 5	—	39	10.3	
370 per day × 5	200 per day × 5	42	33	11
425 per day × 5	20 per day × 5	49	33	
600 per week × 6	500 per week × 6	85	28	12
425 per day × 5	20 per day × 5	87	33	

infusion of 5-FU, followed by a weekly bolus injection, together with three subcutaneous injections of interferon-alfa 2 (Table 4). The response rates are superior to 20% and may reach 40%. Unfortunately, these results have not been compared with 5-FU alone. A large multicentric study (CORFU) comparing 5-FU alone and 5-FU with interferon alfa 2 is presently in the phase of final evaluation.

ADJUVANT 5-FU

Adjuvant 5-FU for colon and rectum cancer was investigated shortly after the introduction of this agent. Two large studies, one by the VASOG Group and one by the COG Group have suggested that 5-FU could have some minor activity. Unfortunately, the methods used in these studies, as well as the statistical analysis, did not reach the required standard of more recent clinical research. Consequently, 5-FU was generally considered inactive as an adjuvant treatment of colon cancer. More recently, a combination of 5-FU and methyl-semustine has been tried in randomised studies. Again, results were controversial, even if a significant prolongation of survival was observed in one of the four studies. These results had a limited impact on the practical use of adjuvant treatment for colon cancer, because of the toxicity and the potential carcinogenic effect of methyl-semustine. Also, 5-FU + methyl-semustine was not tried against 5-FU alone.

Recently, adjuvant treatment of Dukes B and C colon cancer with a combination of 5-FU and levamisole for a duration of one year has been compared with control groups with either surgery alone or surgery followed by levamisole in two large randomised trials [17, 18]. The results of both studies have indicated that the survival was significantly prolonged in patients treated with 5-FU plus levamisole. Unfortunately, the contribution of levamisole as a modulating agent cannot be fully appreciated, because of the absence of a treatment arm with 5-FU alone. As for many previous trials, the authors assumed that, based on available data, adjuvant 5-FU could be considered completely inactive in colon cancer when used alone. Retrospectively, it appears that a 5-FU alone treatment arm would have been as important as the control arm, or even the levamisole arm. Levamisole, an antihelmintic drug with immunostimulating properties, was tried as an adjuvant cancer treatment more than 10 years ago, either alone or combined with radiotherapy or chemotherapy [19], with discordant results that could neither prove nor disprove some effect on survival. In a recent study, the EORTC Group has demonstrated that levamisole alone has no adjuvant effect in colon cancer [20]. Thus, the mechanism of action of levamisole, given together with 5-FU, remains unclear. The speculation that 5-FU alone is responsible for the observed effect on survival in the 5-FU + levamisole trials cannot be excluded. Table 5 summarises the results of levamisole-based adjuvant studies in colon cancer. It is to hope that some more light will be shed onto this disturbing problem when the results of recently terminated or still ongoing randomised trials of adjuvant treatment for colon cancer will be available. In this new generation of studies, various combinations of 5-FU with leucovorin or interferon are compared with 5-FU or 5-FU plus levamisole.

Table 4. 5-FU + alpha-interferon in advanced colorectal cancer

5-FU (mg/m²)	Interferon	No. of patients	Response (%)	Reference
750 per day × 5 (CI) + 750 per week (B)	9MU 3× per week, or 6 or 9 or 12 MU per day	30	47	13
750 per day × 5 (CI) + 750 per week (B)	9MU 3 × per week	45	35	14
750 per day × 5 (CI) + 750 per week (B)	9MU 3 × per week	34	26	15
750 per day × 5 (CI) + 750 per week (B)	9MU 3 × per week	36	42	16

CI = continuous infusion; B = bolus; MU = mega units.

Table 5. Adjuvant levamisole with/without 5-FU in colon cancer

Treatment	Patients	Survival	Reference
Levamisole 100–250 mg days 1 and 2 per week for 1 year	142 (all Dukes C)	Overall: NS Disease free: NS	20
vs. control	145 (all Dukes C)		
Levamisole 150 mg days 1, 2, 3 every 2 weeks for 1 year	130 (35% Dukes B)	Overall: NS (Levamisole + 5-FU vs. C in Dukes C: $P = 0.05$)	17
vs. Levamisole 150 mg days 1, 2, 3 every 2 weeks 5-FU 450 mg/m² per day × 5 for 1 year	136 (33% Dukes B)	Disease free: Levamisole or levamisole + 5-FU vs. C: $P = 0.05$ or less	
vs. control	135 (36% Dukes B)		
Levamisole 150 mg days 1, 2, 3 every 2 weeks for 1 year	310 (all Dukes C)	Overall: Levamisole + 5-FU vs. C: $P = 0.006$	18
vs. Levamisole 150 mg days 1, 2, 3 5-FU 450 mg/m² for 5 days for 1 year	304 (all Dukes C)	Disease free: Levamisole + 5-FU vs. C: $P = 0.0001$	
vs. control	315 (all Dukes C)		

C = control.

Table 6. Adjuvant portal 5-FU in colon cancer

Treatment	Patients	Results	Reference
5-FU + heparin vs. control	257	Fewer liver metastases OS and DFS improved	21
5-FU + heparin vs. urokinase	304	Fewer liver metastases	22
5-FU + heparin vs. control	224	No difference	23
5-FU + heparin vs. control	1158	OS and DFS improved liver metastases unchanged	NSABP Wolmark (1990)
5-FU + heparin + mitomycin vs. control	469	OS and DFS improved liver metastases unchanged	24

LIVER METASTASES

The liver is the most frequent site of tumour extension in case of colon cancer. Although the mechanisms responsible for dissemination and tissue invasion by malignant tumours are still partially unknown, particularly regarding the predominance of metastases in the liver for digestive tract tumours, the speculation of a dominant role of the portal venous circulation in the distribution of secondary tumour deposits is acceptable. The primary objective of intra-portal adjuvant chemotherapy is the destruction of liver micrometastases at a stage of tumour growth still depending on portal blood supply. More mature liver metastases will develop their own vasculature from the arterial blood flow. Following the original study by Tailor and colleagues [21], large randomised trials of intraportal 5-FU, alone or combined, have been activated. Many of them are still in progress or have not yet been published. Table 6 briefly summarises the available results. Similarly to what was observed for systemic intravenous adjuvant 5-FU, these results seem contradictory. Whereas the Mayo/NCCTG study is clearly negative, the original Tailor study shows a benefit in terms of survival and liver extension. Unexpectedly, the two largest studies, by NSABP and the Swiss group SAKK, have observed a prolongation of survival without significant effect on the appearance of liver metastasis. The reason for this remains unclear. Although the biological half-life of 5-FU is short, it cannot be excluded that the adjuvant effect of intra-portal 5-FU is more efficient on extra-hepatic micrometastases than on already established, but still undetectable liver deposits. Although completely speculative, this hypothesis would support the conclusion that systemic 5-FU has an adjunctive antitumour activity. The Swiss group SAKK has recently activated a randomised study comparing identical intravenous and intraportal adjuvant treatments in Dukes B and C colon cancer.

CONCLUSION

In conclusion, FU-based chemotherapy of colon cancer, be it in postsurgical or in advanced stage, produces a limited amount of antitumour effect. The prolongation of survival in adjuvant studies, in comparison with a control group, is too small to be easily objectivated in randomised trials with a few hundred patients. In advanced stages, the rate of objective response is 20% or less. Higher response rates have been obtained when the activity of FU is improved by long term infusion or by biochemical modulation. It is hoped that modulating agents will also improve the adjuvant effects of FU in patients with colon cancer.

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