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Current Chemotherapeutic Possibilities in the Treatment of Colorectal Cancer

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To date, the best treatment modality for colorectal cancer is a surgical excision of the primary tumour. Adjuvant therapy can be added to the surgical treatment and can consist of adjuvant chemo-, immuno- or radiotherapy. In the U.S.A., adjuvant chemotherapy with 5-fluorouracil (5FU) and levamisole is advocated as standard treatment for patients with localised poor risk (Dukes stage C) colon cancer. Not every clinician is convinced of the usefulness of adjuvant chemotherapy. Therefore, confirmatory clinical trials are still ongoing to compare no adjuvant treatment with 5FU/levamisole adjuvant treatment. Treatment with 5FU/leucovorin has been shown to be effective as adjuvant therapy. In rectal cancer, radiotherapy can be added to the primary surgical treatment. It is still unproven whether radiotherapy should be given pre-, peri, or postoperatively, and whether chemotherapy should be added to this multimodality regimen. If chemotherapy is applied as a radio-sensitiser, a continuous infusion is preferable to daily bolus injection. Much effort has been put into the improvement of the response rate of 10–15% 5FU, used as a single agent in the treatment of advanced colorectal cancer. Biochemical modulation of 5FU with leucovorin and interferon, different schedules of 5FU administration and hepatic arterial therapy have all been attempted. Higher response rates have been reported with these treatment modalities, unfortunately without improvement of survival, except for the intra-arterial approach. Recently, two new drugs have shown efficacy in the treatment of advanced colorectal cancer. A phase II trial with Tomudex (ZD1694), a new antifolate thymidylate synthase inhibitor, produced a response rate of 25% in patients with advanced colorectal cancer. A phase II trial with CPT-11, a topoisomerase I inhibitor, produced a response rate of 27% in patients with advanced disease and 25% response in patients with prior chemotherapy.

Key words: colorectal cancer, chemotherapy
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INTRODUCTION

COLORECTAL CANCER is second only to lung cancer in men and to breast cancer in women as a cause of cancer death in the Western world. Epidemiological data from the Dutch cancer registry show an incidence of 7000 new cases for colon and rectal cancer and a death rate of 4000 per year. In the U.S.A., 155 000 new cases are diagnosed every year. Adenocarcinoma of the large bowel affects approximately one person in 20 in the U.S.A. and in most Western countries. In this paper, we will give an overview of the current chemotherapeutic possibilities for colorectal cancer. The focus will be on two main topics: treatment of colorectal cancer in the adjuvant setting and treatment of metastatic disease.

ADJUVANT THERAPY FOR COLORECTAL CANCER

The therapy of first choice for patients with colorectal cancer is radical surgery of the primary tumour. Adjuvant therapy is added to surgery, and consists of chemotherapy, radiotherapy or immunotherapy. Currently, there is still controversy concerning the usefulness of adjuvant chemotherapy. Although this treatment is considered standard in many countries for patients with Dukes stage C colon cancer, in the Netherlands a confirmatory trial with a no treatment arm is still ongoing.

Adjuvant chemotherapy

The first adjuvant chemotherapy trials in colorectal cancer date back to the 1960s. Single agent (most frequently 5-fluorouracil) or combination chemotherapy studies have never shown any significant survival benefit for patients receiving adjuvant chemotherapy. One of the reasons for the negative results may have been the low dose intensity of therapy which was used in these trials. In 1990, Moertel and associates reported the results of adjuvant 5-fluorouracil (5FU) and levamisole in colon cancer patients, and these data were considered as a breakthrough in the history of the adjuvant studies [1]. In 1974, a study from Verhaegen had already been published in which levamisole, an old veterinary antihelmitic drug, was used as an anticancer agent. The rationale to use levamisole as an anticancer agent was the immunomodulatory effects of this drug observed in mice. In the Moertel study, 318 patients with stage B were randomised for surgical treatment alone or surgery combined with 5FU/levamisole. Treatment for the 929 stage C colon cancer patients consisted of three arms; surgery alone, surgery plus levamisole or surgery plus 5FU/levamisole. Chemo-

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therapy was planned for administration for 1 year. The overall death rate was reduced by 33% and the risk of recurrence was reduced by 41% in patients with stage C who had been treated with 5FU/levamisole [1–3] (Figure 1).

Recently, some concern has arisen regarding toxicity associated with adjuvant 5FU/levamisole. Central nervous system as well as hepatic toxicity have been reported. This central nervous system toxicity consisted of clinical symptoms such as personality changes, disorientation, focal neurological signs and seizures. Radiological abnormalities based on gliomatosis, granulomatous changes and demyelination have been observed. A total of 5 patients with this syndrome has been reported in the literature thus far. Clinical and radiological changes improved when 5FU/levamisole was discontinued and steroids were administered [4]. A more frequently occurring phenomenon is hepatic toxicity, with elevation of alkaline phosphatase, transaminases or bilirubin. Liver function disturbances were reported in 61.2% of the patients treated with 5FU/levamisole. This toxicity is usually mild and subsides when the therapy is discontinued. Although the changes are asymptomatic and reversible, this hepatic toxicity may mimic laboratory abnormalities that are frequently observed when hepatic metastases are present [5].

Adjuvant studies with 5FU and leucovorin have also been conducted. A randomised trial in which 1041 patients with Dukes stage B and C colon cancer were treated with MeCCNU, vincristine and 5FU (MOF) or 5FU/leucovorin showed a favourable outcome for patients treated with 5FU and leucovorin [6]. The 3-year disease-free survival rate for patients in the 5FU/leucovorin arm was 73% and for patients treated with MOF it was 64% ($P<0.05$). The overall survival rate was 84% for patients treated with 5FU/leucovorin and 77% for the MOF treated group ($P<0.05$) (Figure 2). Some trials in which 5FU/leucovorin was tested versus a no treatment arm have been prematurely closed because the National Institutes of Health consensus concluded that 5FU/levamisole is the standard treatment. Randomised studies are ongoing with four treatment arms; 5FU/levamisole versus 5FU/high dose leucovorin and 5FU/low dose leucovorin versus 5FU/levamisole/leucovorin. The studies described above suggest that 5FU/leucovorin may also be effective as adjuvant therapy in colon cancer.

At this point, we can conclude that we still do not know whether adjuvant chemotherapy for colon cancer is beneficial. The mechanism of action, dose and schedule of the combination of 5FU/levamisole have still to be defined. It is not known which patient groups will benefit from adjuvant chemotherapy, patients with stage B and/or C colon cancer. Therefore, new parameters to select patients who will benefit from adjuvant therapy are urgently needed. Recently, a report described the value of thymidylate synthase, the target enzyme of 5FU, to predict the result of 5FU therapy in rectal cancer patients [7]. So far, the role of tumour suppressor genes (e.g. *TP53*) or oncogenes (e.g. *CMYC*) as predictive factors for the response to chemotherapy is not clear.

In rectal cancer, adjuvant treatment can consist of two modalities, adjuvant radiotherapy alone or combined with adjuvant chemotherapy. It is still not clear when to use adjuvant radiotherapy, pre- or postoperatively, and whether radiotherapy needs to be combined with chemotherapy. The consensus conference of the National Institutes of Health indicated postoperative pelvic irradiation and chemotherapy as standard treatment for stage II and III rectal cancer patients [3]. A study by Krook and associates, in 204 patients with rectal cancer, showed a longer disease-free interval and an improved overall survival in patients treated with chemotherapy (5FU) plus radiotherapy compared to patients treated with radiotherapy alone [8]. Protracted 5FU infusion during postoperative irradiation of the pelvis produced a significantly longer recurrence-free survival and a significantly improved overall survival compared with standard systemic administration of 5FU, in 660 patients with high risk rectal cancer stages II and III [9]. A randomised trial in 413 patients showed a local failure in 12% of the patients treated with pre-operative radiation therapy, compared with 21% local failures in patients with postoperative radiation therapy. New randomised studies are being carried out based on previous reports in which peri-operative radiation therapy is combined with 5FU/leucovorin chemotherapy (Int R9401 and NSABP RO-3) [10].

Adjuvant immunotherapy

The rationale for this treatment modality came from a guinea pig hepatocarcinoma model which showed that BCG mixed with syngeneic tumour cells can induce systemic immunity, resulting in elimination of tumour cells. A total of 80 patients with stage B_2–C_3 colon or rectal cancer were randomised into a resection only group or a treatment group with resection plus an

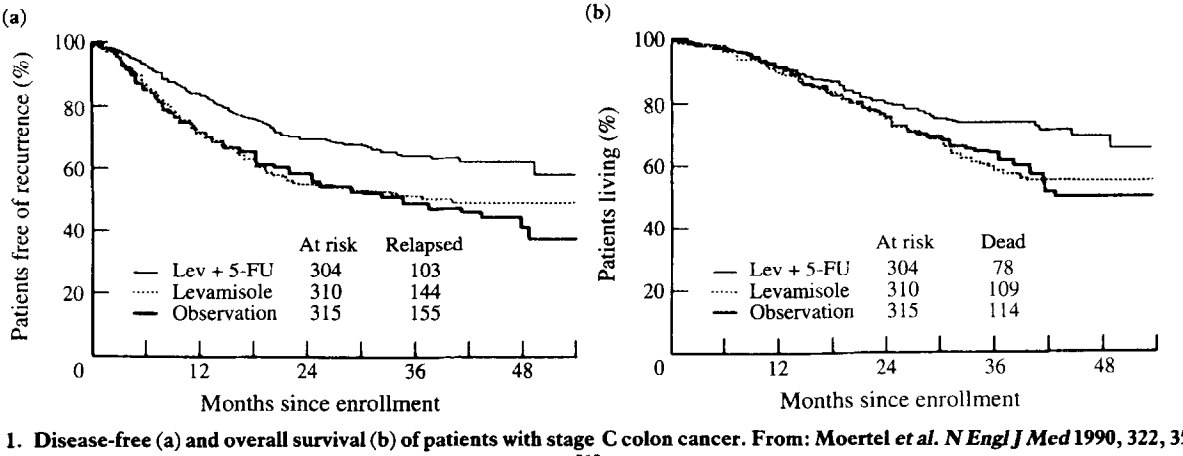

Figure 1. Disease-free (a) and overall survival (b) of patients with stage C colon cancer. From: Moertel *et al.* *N Engl J Med* 1990, 322, 358–362 [1].

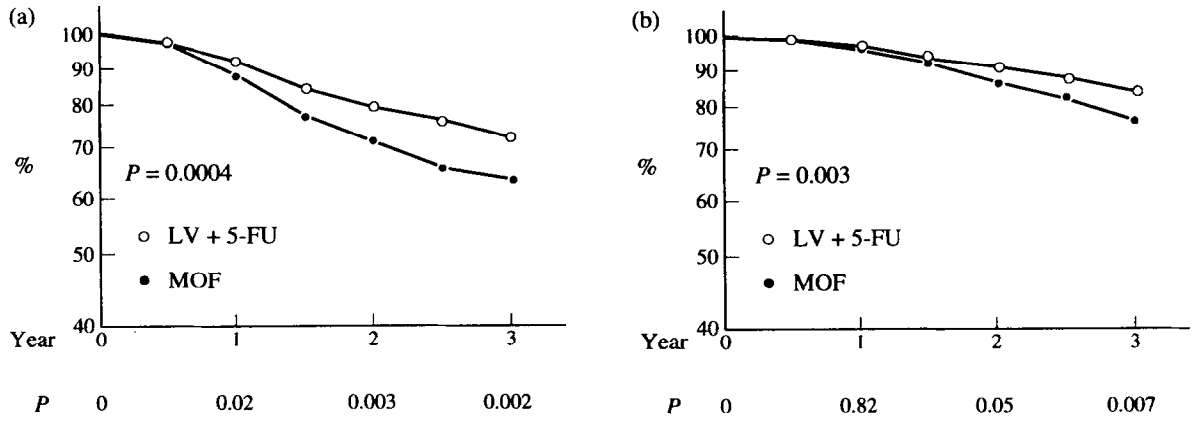

Figure 2. Disease-free (a) and overall survival (b) of patients with stages B and C colon cancer [6].

autologous tumour cell vaccine. A significant improvement in disease-free and overall survival for colon cancer patients was found. No improvement for rectal cancer patients was seen [11]. Further studies to confirm these data are ongoing in larger patient groups. This treatment is generally well tolerated and the most important side effect is a local skin reaction. An important drawback of this approach is the difficulty of the tumour vaccine preparation. In a confirmatory multicentre trial, co-ordinated at the Free University Hospital in Amsterdam, patients with colon cancer stages B and C are included.

CHEMOTHERAPY IN ADVANCED COLORECTAL CANCER

Unfortunately, since 1957, no cytotoxic agent with a better therapeutic index than 5FU for the treatment of advanced colorectal cancer has been developed. The main mechanism of action of 5FU is inhibition of thymidylate synthase (TS) by the active metabolite FdUMP, resulting in disruption of DNA synthesis. The response rate of 5FU as a single agent is low at 10–15%. Therapy with 5FU has no impact on overall survival. Attempts are being made to improve the response rates of 5FU by combining 5FU with other agents, by changing the schedule of 5FU administration or by locoregional therapy.

Biochemical modulation of 5FU

Biochemical modulation is the use of a pharmacological agent to increase the biological effect of a second drug by producing a selective enhancement of antitumour activity or a selective protection of the host [12]. Various agents such as methotrexate, PALA, leucovorin and interferons have been used to modulate 5FU activity. The most efficient modulator known is leucovorin. The mechanism of modulation of 5FU by leucovorin is based on stabilisation of the ternary complex of TS with FdUMP by a folate cofactor, for which leucovorin is the external source. In experimental and clinical studies, enhancement of TS inhibition after administration of 5FU/leucovorin compared with 5FU alone has been demonstrated [13, 14].

Randomised trials have been performed comparing 5FU/leucovorin with 5FU single agent treatment [15]. Response rates from 16 to 45% have been reported for patients treated with 5FU/leucovorin. When meta-analysis of a large number of studies was performed, an increased response rate of 23% was found in the 5FU/leucovorin treated patients versus 11% in the single agent 5FU group. However, survival analysis failed to show any benefit from the combination treatment [16] (Figure 3). There is still much uncertainty regarding the schedule and the dose of leucovorin. Different studies have evaluated a variety of schedules: high dose leucovorin (500 mg/m^2), "standard" dose leucovorin (200 mg/m^2) and low dose leucovorin (20 mg/m^2). However, one schedule has not been adopted as superior to another. The side effects of 5FU/leucovorin mainly occur to the gastro-intestinal tract, resulting in mucositis and diarrhoea.

The cytotoxic effect of 5FU may also be modulated by interferons. Suggested mechanisms of interactions between 5FU and interferon-α include an increased formation of FdUMP, inhibition of 5FU-induced upregulation of thymidylate synthase (TS) and others. Synergistic cytotoxic activity of 5FU and interferon has been shown *in vitro* [17]. Phase II clinical trials have resulted in response rates ranging from 26 to 63% for combined 5FU and interferon-α [18]. Conclusive results of phase III trials have yet to be reported.

The use of multiple modulating agents to potentiate 5FU activity through different biochemical pathways is theoretically attractive. A phase II study in 46 patients of 5FU, leucovorin and interferon-α_{2a} reported a response rate of 54% with metastatic colorectal cancer. The addition of interferon-α_{2a} to 5FU/leucovorin treatment gave manageable non-haematological toxicity. The disease-free survival was 7.8 months and the overall survival 16.3 months [19, 20]. These data are promising, but randomised trials are needed for a definitive evaluation of the value of this and other combinations.

Prolonged infusion of 5FU

Continuous i.v. infusion of 5FU can be given during a period of months. Clinical studies of this modality performed in the last few years reported response rates of 30–40%. A higher dose of 5FU can be delivered by this method compared with bolus injection [21]. No improvement of survival has been shown when continuous infusion was randomly compared with bolus administration [22]. An important drawback of this method of 5FU administration is that it is technically complicated. Currently, this method of 5FU administration cannot be recommended in routine daily practice.

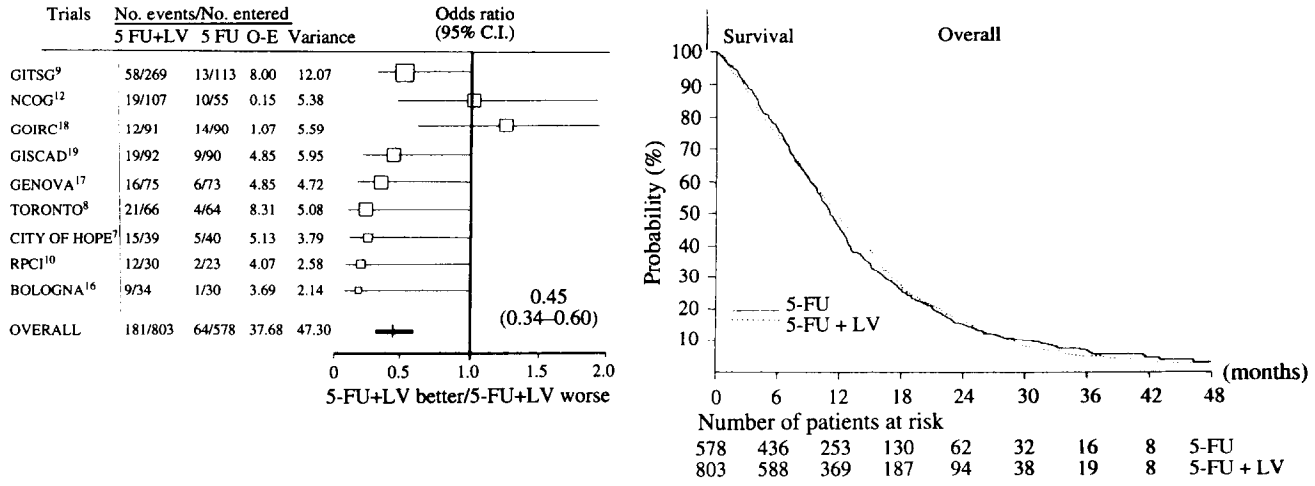

Figure 3. Odds ratios of response rates and overall survival from the meta-analysis of patients treated with 5FU/leucovorin. From: Meta-analysis project group. *J Clin Oncol* 1992.

5FU can also be given as chronotherapy. Based on biorhythm, chemotherapeutic agents are administered in circadian-altered regimens. In this way, a higher dose intensity can be reached and doses are lower during the period of the day when mucosa and bone marrow are actively synthesising DNA so side effects will be less serious. A recent study comparing chronomodulated versus continuous infusion with oxaliplatin, 5FU and leucovorin in patients with metastatic colorectal cancer produced promising results [23]. However, it must be realised that drug administration with chronomodulation is very complex and can only be performed in specialised centres. The most effective schedules based on chronomodulation have still to be established in clinical trials.

Hepatic arterial infusion

Hepatic arterial infusion of chemotherapy is an attractive method to test the concept of dose–effect relationship in colorectal carcinoma. The high total body clearance and high extraction rate of fluoropyrimidines makes these drugs the most suitable for this approach. A 100 to 400-fold increase of FUdR and a 50 to 100-fold increase in 5FU pharmacokinetic advantage is seen after hepatic arterial infusion compared with peripheral infusion [24]. Response rates of hepatic arterial chemotherapy are significantly higher (42–62%) than those of systemic therapy (10–21%) [24]. The arterial treatment with FUdR may produce complications such as biliary sclerosis, chemical hepatitis, gastric ulceration and cholecystitis. Problems with access systems are of concern [25]. A recent study showed a significant prolongation of survival (median 405 versus 226 days) with normal quality of life in the 39 FUdR treated patients compared with the 46 control patients who did not receive hepatic arterial chemotherapy [26]. Dexamethasone is sometimes added to the hepatic arterial chemotherapy with the aim of reducing the frequency of sclerosing cholangitis. Studies on modulation of hepatic arterial FUdR with leucovorin are ongoing. The preliminary results showed an increase in toxicity.

New drugs

New active drugs in the treatment of colorectal cancer are the novel TS inhibitors and the camptothecan derivative CPT-11. These new TS inhibitors are antifolates and inhibit TS at the folate binding site. Encouraging results have been reported with Tomudex (ZD1694), in a phase II study with 124 patients with advanced colorectal cancer; a response rate of 25% was observed [27]. Patients had no prior chemotherapy for advanced disease, and only 6 patients had received prior adjuvant chemotherapy with 5FU. Side effects included were neutropenia, diarrhoea, nausea and vomiting and fatigue. Phase III trials are currently ongoing.

The other promising new drug, CPT-11, is a potent inhibitor of topoisomerase I. To be active, CPT-11 must be converted to the active metabolite SN-38. A phase II study showed a partial response rate of 27% in 63 patients with metastatic colorectal cancer. The 51 patients who had received prior radiotherapy or chemotherapy showed a 25% response [28]. Diarrhoea and neutropenia were the dose-limiting toxicities. CPT-11-induced diarrhoea can be divided into early and delayed diarrhoea. The early diarrhoea occurs during or shortly after the infusion of CPT-11. The delayed diarrhoea occurs 4–8 days after infusion, and seems to be a secretory diarrhoea which can be treated with high dose loperamide. It may be of interest to combine CPT-11 with 5FU. Recently, a pharmacokinetic study has been performed in 12 patients who received CPT-11 followed by a continuous infusion of 5FU. A change in the pharmacokinetics of CPT-11 and SN-38 was observed, a decrease in the AUC of CPT-11 and an increase in the AUC of SN-38 [29]. These results are too preliminary to draw any conclusions on the efficacy of the combination of CPT-11 with 5FU. The toxicity shown in the combination treatment was mild which is promising. Clinical trials in which the combination of CPT-11 and 5FU is further assessed are ongoing in the U.S.A. and France. Preliminary results have not yet been published.

CONCLUSION

Since the synthesis of 5FU in 1957, much has been done to improve the response and survival rate with 5FU as a single agent in advanced colorectal cancer. Improvements in response rates have been documented by modulating 5FU with leucovorin or interferons, by administration of 5FU as a continuous infusion or as chronotherapy or by locoregional therapy. However, none

of these new directions in chemotherapeutic possibilities in colorectal cancer have led to an increase in survival. It is difficult to predict what we can expect from new drugs, such as ZD1694 and CPT-11, in the treatment of colorectal cancer. However, the results of 5FU modulation with leucovorin and interferon are promising.

For adjuvant therapy, results have been obtained with the use of 5FU/levamisole and 5FU/leucovorin in patients with stage C. In the U.S.A. and many other countries, 5FU/levamisole is used as standard adjuvant treatment for patients with stage C colon cancer. In other countries, such as the Netherlands, there is no consensus that adjuvant treatment is of benefit.

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