5-fluorouracil modulation in palliative chemotherapy for colorectal carcinoma
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Colorectal carcinoma is the second most common malignancy in western countries. The overall five-year survival rate for this malignancy is about 45%. The prognosis depends markedly on the extent of disease at time of diagnosis: patients with a carcinoma restricted to the bowel wall have a 5-year survival of 90%, but those patients with distant metastases have a median survival of 10.5 months. In selected patients with liver metastases surgical removal of these metastases results in prolonged survival. If such options are not possible, these patients may be offered systemic chemotherapy. Among the numerous drugs tested, the fluorinated pyrimidine 5-fluorouracil (5-FU) is the most active agent. However, only 10-20% of the patients will respond to monotherapy 5-FU and effects on survival are discouraging low. Therefore, reducing the mortality from colorectal cancer should be aimed at prevention, screening leading to earlier detection, and better chemotherapeutic regimens. This thesis is focused on ways of enhancing 5-FU based chemotherapy.

In chapter 1 the general outlines of this thesis are described, with emphasis on the mechanism of cytotoxicity of 5-FU.

In chapter 2 an update is given of recent developments in the field of colorectal carcinoma. The past decade has provided growing insight into three basic components of cancer genetics: oncogenes, tumor suppressor genes and the concept that malignant cells arise from genetic alteration of a normal cell. The formation of colon adenomas and carcinomas appears to be associated with a series of such genetic alterations. The familial polyposis coli gene is thought to be responsible for the development of adenomas from normal mucosa. Subsequent chromosomal changes leading to development of carcinoma may be caused by environmental mutagens. In addition to this genetic theory, numerous risk factors for developing colorectal cancer have been identified. These risk factors are associated with an increased proliferative state of the entire colonic mucosa. These proliferation changes may precede colorectal cancer. It has also been suggested that reduction of the mitotic changes may prevent cancer. However, its exploitation in reducing cancer risks will take considerable efforts in clinical practice.

Screening is aimed on detection of earlier stages of colorectal cancer, but the costs of screening the average population are high, and therefore screening is still a controversial issue. The mucosal proliferation rate, preneoplastic gene expression and genetic screening may in future be useful to determine a subgroup eligible for intensive screening strategies.

The finding of a 30% survival advantage in patients with colon cancer penetrating the bowel wall with affected lymph nodes (Dukes C) receiving 5-FU plus levamisal has been a major step forward. Whether this regimen or other 5-FU based adjuvant therapies will be the most effective for these patients, and whether such therapy is also useful in patients with Dukes B
carcinoma (no affected lymph nodes), will in the near future more clearly be established. Presently, locoregional colorectal cancer may be considered a disease benefiting surgical adjuvant therapy.

The developments discussed in this chapter may have far reaching consequences for the prevention, early detection and early chemotherapeutic treatment of colorectal cancer. Each of these developments may be a step ahead in the reduction of mortality of this disease.

Chapter 3 contains the results of a phase II study of 5-FU continuous infusion 600 mg/m\(^2\)/24 hours day 1-4 preceded by a high dose methotrexate 1,500 mg/m\(^2\) rapid infusion in patients with advanced colorectal carcinoma. In 21 patients who had not been treated previously with other chemotherapeutic agents, an overall response rate of 20% was observed. Twelve patients with progression of tumor during this chemotherapy regimen, subsequently received the same dose of 5-FU combined with daily leucovorin 200 mg/m\(^2\) i.v. on day 1-4. Two out of these 12 patients had stabilization of tumor growth. Mucositis grade 1-2 occurred in 50% of patients during both regimens. Other toxicities were limited, the chemotherapy was well tolerated. Median survival of the 21 patients was 10 months. It was concluded that high dose methotrexate combined with 5-FU continuously infused has activity in colon cancer. However, the response rate is still low and improvement of survival is unlikely to occur. The observation of stabilization of disease after substituting methotrexate by leucovorin underlines the differences in 5-FU modulation, but its clinical value for patients resistant to methotrexate plus 5-FU is clearly limited.

In chapter 4 a phase I and phase II study of 14 days continuous infusion of 5-FU combined with weekly leucovorin is described. Prolonged infusion of a cytostatic drug allows exposure of tumor cells over the course of one or more doubling times. In patients with metastatic colorectal cancer, treatment with continuously infused 5-FU results in improved response rates and decrease side effects as compared to bolus injection 5-FU. Leucovorin addition to 5-FU diminishes resistance to this drug by providing reduced folates, necessary for increasing fluoropyrimidine mediated thymidylate synthase inhibition (see also Figure 1, chapter 1). Several clinical studies in patients with colorectal cancer treated with 5-FU/leucovorin demonstrated not only improved response rates but also improved survival. In the present study both adaptations (continuous infusion and co-treatment with leucovorin) are combined. The phase I study was performed to establish the maximum tolerated dose of a weekly intravenously administered leucovorin injection when combined with a 5-FU dose of 300 mg/m\(^2\)/24 hours continuously infused for 14 days. Courses were repeated every four weeks. The addition of any dose of leucovorin starting with 20 mg/m\(^2\) to this 5-FU dose resulted in an unexpectedly high
toxicity. Therefore, we decided to lower the 5-FU dose to 200 mg/m²/24 hours for 14 days. It appeared feasible to combine this with a weekly bolus injection of 200 mg/m² leucovorin. At this dose level 21 patients with metastatic colorectal cancer were treated. None of these patients received prior chemotherapy. In these 21 patients one patient had a complete response (disappearance of all perceptible tumor) and four patients had a partial response (at least 50% reduction of largest lesion with no progression of other lesions). This gives a response rate of 24%. Toxicity of this regimen was low: mucositis WHO grade 1-2 was most frequent, and observed in 32% of chemotherapy courses. It was concluded that this continuous infusion regimen has comparable antitumor response to other 5-FU/leucovorin regimens in colorectal carcinoma. This regimen has minimal toxicity.

As described above, the effect of leucovorin on the fluoropyrimidines 5-FU and 5-fluoro-2' deoxyuridine (FUdR) has a well known basis: increasing the degree and retention of fluoropyrimidine mediated inhibition of a key enzyme in DNA synthesis (thymidylate synthase) (see Figure 2, chapter 1). Synergism has also been described between 5-FU and α-interferon. The mechanism has not yet been elucidated, but may also be mediated by thymidylate synthase inhibition. Besides, very limited data are available on combined effects of leucovorin and α-interferon on fluoropyrimidines.

In chapter 5 the modulating effects of leucovorin and/or α-interferon were studied in the human colorectal cancer cell lines SW 948 and COLO 320. Also thymidylate synthase levels were studied in both cell lines, as well as the effects of 5-FU and α-interferon on this enzyme. Although both cell lines have a colorectal cancer origin, striking differences were noted: the SW 948 cell line was 11.7 fold more sensitive to 5-FU and 16.7 fold more sensitive to FUdR compared to the COLO 320 cell line. Differences between fluoropyrimidine sensitivity correlated with lower thymidylate synthase level in the more sensitive cell line. In COLO 320 modulation of 5-FU, either by leucovorin or by α-interferon was not possible. As leucovorin did enhance FUdR activity in this cell line, it is conceivable that 5-FU mediated cytotoxicity in COLO 320 is not primarily mediated by thymidylate synthase inhibition. In SW 948 addition of leucovorin to 5-FU resulted in a 2.4 fold lower IC₅₀ (concentration 5-FU required to induce 50% growth inhibition), compared to 5-FU alone. α-Interferon lowered the IC₅₀ of 5-FU 6.8 fold in this cell line, and the IC₅₀ on the combination 5-FU, leucovorin and α-interferon was 11.2 fold lower as compared to 5-FU alone. In this cell line, the effects of both drugs on FUdR were comparable, but less pronounced. Although direct effects of α-interferon on thymidylate synthase could be excluded, evidence existed that α-interferon, when combined with fluoropyrimidines, must have indirect effects on this enzyme. The cell lines here described can...
serve as a model for successful or failing modulation of 5-FU by leucovorin and/or α-interferon. It may be possible to select sensitive or resistant tumors by measuring thymidylate synthase levels. The finding that α-interferon can increase 5-FU/leucovorin mediated cytotoxicity, justifies further study of the triple agent combination in phase I-II studies in patients with advanced colorectal carcinoma.

In chapter 6 the toxicity (phase I study) and activity (phase II study) of the addition of α-interferon to a 5-FU/leucovorin combination is described. We started the phase I study with determining the optimal 5-FU dose (bolus injection, two consecutive days) when combined with a fixed oral dose leucovorin (60 mg, 3 times daily). Thereafter, the optimal dose of 5-FU with the same dose leucovorin, combined with 18.10^6 Units α-interferon was established. The modulating agents leucovorin and α-interferon were given for three days, starting one day before 5-FU infusion and ending at the last day of 5-FU infusion. Chemotherapy was given every two weeks. Serum levels of leucovorin and its active metabolite were measured in order to find out whether the concentrations of these reduced folates were high enough to modulate 5-FU cytotoxicity. Besides, the influence of α-interferon on pharmacokinetic behaviour of leucovorin could be studied by comparing the serum levels of reduced folates in patients treated with and without α-interferon. The phase I study was followed by a phase II study of 5-FU/leucovorin/α-interferon at the established optimal dose of 5-FU in patients with disseminated colorectal cancer who did not receive prior chemotherapy.

In the phase I study an optimal dose of 750 mg/m^2/day 5-FU was found for the 5-FU + leucovorin combination. Dose limiting toxicities were mucositis, diarrhea and leucopenia. Although α-interferon added its own toxicity (fever, flu like symptoms), it did not influence the optimal dose of 5-FU. Pharmacokinetics of repeated oral dose of 60 mg leucovorin, started one day before 5-FU infusion, revealed mean peak and through serum concentrations of reduced folates high enough to modulate in vitro 5-FU cytotoxicity. Significantly higher serum levels were found after addition of α-interferon. Influence of α-interferon on gastrointestinal absorption or on renal clearance of leucovorin could be excluded, and thus an effect of α-interferon on (hepatic) metabolism of leucovorin is probable. In the phase II study on the triple drug combination a complete response was observed in 3 patients and a partial response in 12 out of 28 patients (response rate: 15/28 patients = 54%). Median survival in this study was 16 months. Although the response rate is encouraging, median time to progression of responding patients after completion of chemotherapy was only 20 weeks. The frequently observed, sometimes severe, toxicity made prolonged treatment after eight chemotherapy courses not feasible. In an attempt to increase response duration, a less toxic maintenance
therapy is now given to responding patients. This treatment is equal to the above described 3 day regimen, but it is given every six weeks in stead of every two weeks. It is concluded in this chapter that this 5-FU/leucovorin/α-interferon combination seems active in metastatic colorectal carcinoma. The pharmacokinetic interaction between α-interferon and leucovorin may play a role in the activity of this regimen. Proof of superiority to other schedules requires larger randomized trials.

In conclusion, the results of palliative chemotherapy for patients with disseminated colorectal carcinoma can be improved. The effect of 5-FU, for decennia the only drug that occasionally produced responses, can be augmented by at least two drugs: leucovorin and α-interferon. On the combination of 5-FU and leucovorin a small but significant improvement of survival has been demonstrated. The chemotherapy is compatible with a satisfactory quality of life by giving low doses leucovorin or by giving the 5-FU as a prolonged infusion. On the combination of 5-FU and α-interferon high response rates have been documented, and results of phase III studies are now awaited. The demonstration of increased 5-FU/leucovorin mediated cytotoxicity after the addition of α-interferon, and the observation of a high response rate on a 5-FU/leucovorin/α-interferon combination (at the cost of high toxicity), indicates that further improvement of treatment strategies for disseminated colorectal cancer may be in finding an optimal regimen on this triple drug combination.