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Report

Prevention and treatment of peritoneal carcinomatosis in experimental investigations with CPT-11 and oxaliplatin

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Following surgical resection of colorectal carcinoma, local recurrence in the tumor bed or in the mesentery remains a frequently encountered problem. Currently there are no recognized standard therapy protocols for the prevention of local recurrence or the treatment of peritoneal carcinomatosis. The aim of our trial was to investigate whether CPT-11 and oxaliplatin could decrease i.p. tumor growth in a basic experimental animal model. Experiments were performed on three groups of animals plus controls. In the first group, the cytostatic agents were applied directly following tumor cell implantation into the peritoneal cavity. In the second group, early postoperative i.p. chemotherapy (days 5, 10 and 15 following surgery) was administered. In the third group, late i.p. chemotherapy (days 15, 20 and 25 after tumor cell transfer) was administered with the intention of reducing a manifest peritoneal carcinomatosis. The trial also set out to describe any side effects observed following i.p. administration. The results indicated that CPT-11 and oxaliplatin were highly effective in reducing i.p. tumor spread after direct i.p intraoperative application. Intraperitoneal administration of CPT-11 or oxaliplatin also decreased i.p. tumor growth after early i.p. chemotherapy. CPT-11 was a little more effective with lower side effects. However, it was clear that it was not possible to treat a manifest peritoneal carcinomatosis in this way. [© 2002 Lippincott Williams & Wilkins.]

Key words: Animal study, colorectal carcinoma, CPT-11, oxaliplatin, peritoneal carcinomatosis..

Introduction

Throughout the world, carcinoma of the large bowel is one of the most common malignant diseases. It is estimated that 15 000 people in France[1] and 58 000 people in the US[2] die of colon carcinoma each year. In Germany, 50 000 new cases of colon carcinoma were noticed each year.[3]

There are two major unsolved problems regarding the treatment of colon carcinoma. The first concerns the frequency with which peritoneal carcinomatosis occurs. Indeed, peritoneal carcinomatosis is sometimes the first symptom in the evolution in colon carcinoma. Sugarbaker[4] reported peritoneal carcinomatosis as the colon carcinoma recurrence site in 50% of cases. In a French registry of digestive tumors, 107 out of 1012 patients presented with peritoneal carcinomatosis at the time of first diagnosis.

The other unsolved problem is the high local recurrence rate in the tumor bed or in the nearby mesentery after surgical resection of colorectal carcinoma. The reported local and distant recurrence rate of colon cancer after curative surgical resection is between 8.5 and 25.6%.[5–12] In most of these cases it is impossible to perform a second curative tumor resection.

Recently there have been reports of the benefits of i.p. chemotherapy in advanced gastric and colorectal cancer.[13–23] In the treatment of colorectal cancer, i.p. 5-fluorouracil (5-FU) has been the most commonly used agent either in combination with leucovorin or alone.[17,18] Mitomycin and cisplatin were the preferred cytostatic agents in i.p. chemotherapy of gastric cancer.[19–22] However, there are problems regarding the results of trials using all these agents; few of these trials were randomized and patient numbers were very small. Thus, today there are no standard therapy protocols for the prevention of local recurrence or the treatment of peritoneal carcinomatosis.

CPT-11 and oxaliplatin are relatively new cytostatic agents, but both have been shown to provide benefits in the treatment of patients with advanced

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colorectal cancer.[24–27] The aim of the trial was to investigate whether CPT-11 or oxaliplatin could decrease i.p. tumor growth in a basic experimental animal model.

Experiments were performed on three groups of animals plus controls. In the first group, the cytostatic agents were applied directly following tumor cell implantation into the peritoneal cavity. This group simulates the clinical situation with free cancer cells on the peritoneal surface. In the second group, early postoperative i.p. chemotherapy took place to simulate the clinical situation with early established microscopic implants. In the third group, late i.p. chemotherapy was administered with the intention of reducing a manifest peritoneal carcinomatosis with visible tumor nodules.

The trial also set out to detect any differences between the two cytostatic agents with respect to i.p. anti-tumor growth and to describe any side effects following i.p. administration.

Materials and methods

Animal model

For the studies on the prevention of peritoneal carcinomatosis, we used an animal experimental model that was standardized in our hospital by Pross *et al.*[28] The animals used were adult male WAG/RIJ rats (Harlan, Borchen, Germany). The animals weighed 240–250 g and were kept under standard conditions (free access to pelleted chow and water, 24°C room temperature, 12 h day/night cycle) in the experimental animal laboratory.

Prior to the experimental surgical intervention, animals fasted for 12 h. The planned animal experiment (prophylaxis of peritoneal carcinomatosis) was submitted to the animal protection authority of Sachsen-Anhalt-Dessau for examination and subsequently approved under the number: Chir/G/4-99.

Tumor cell implantation and cytostatic treatment

The adenocarcinoma cell line CC-531 (Cell-Lines Service, Heidelberg, Germany) was employed for the induction of peritoneal carcinomatosis. These immunocompetent tumor cells stem from a moderately differentiated colon carcinoma induced by 1,2-dimethylhydrazine and are capable of inducing tumor growth in WAG rats. Under standardized conditions the CC-531 cells were cultured in a medium of RPMI 1649 (Gibco, Eckstein, Germany) to which 10% heat-inactivated FBS (Gibco) and antibiotics/antimycotics (Life Technologies, Karlsruhe, Germany) had been added at 37°C in a CO_2 incubator. Cells were counted in a Coulter Counter Z II (Coulter Immunotech, Marseille, France). Cell viability was confirmed with the Trypan blue exclusion test using a Neubauer chamber.

In 24 animals, implantation of the tumor cells was effected via a laparotomy performed under general anesthesia. Implantation of the adenocarcinoma cells CC-531 at a concentration of 5×10^6 cells was effected directly into the region of the mesentery trunk. The body surface for the animals was between 0.03 and 0.04 m^2 [formula: $A\ (m^2) = m_k^{0.425} \times l_K^{0.725}/139.315$].

The following concentrations for the cytostatic agents were chosen (Table 1): CPT-11, 300 mg/m^2, 8.5 and 9.5 mg/animal; oxaliplatin, 60 mg/m^2, 1.8–2.4 mg/animal.

Therapy and control groups

Group I Five minutes after tumor cell implantation the animals in group I-A received i.p. CPT-11 ($n = 6$) and those in group I-B ($n = 6$) received i.p. oxaliplatin. This group simulated the direct intraoperative situation with free cancer cells on the peritoneal surface.

Group II An i.p. Portsystem (Figures 1 and 2) was implanted after tumor cell application in all animals. In group II-A (CPT-11/$n = 6$) and group II-B (oxaliplatin/$n = 6$), active drugs were administered on days 5, 10 and 15 after tumor cell implantation. This experimental group simulated the i.p. treatment of early established microscopic implants.

Group III In group III-A (CPT-11/$n = 6$) and group III-B (oxaliplatin/$n = 6$), active drugs were applied

Table 1.

Group	Drug	Animals per group *N*	Concentration (mg/m^2)
I-A, II-A and III-A	Irinotecan (Aventis)	6	300
I-B, II-B and III-B	oxaliplatin (Sanofi-Synthelabo)	6	60

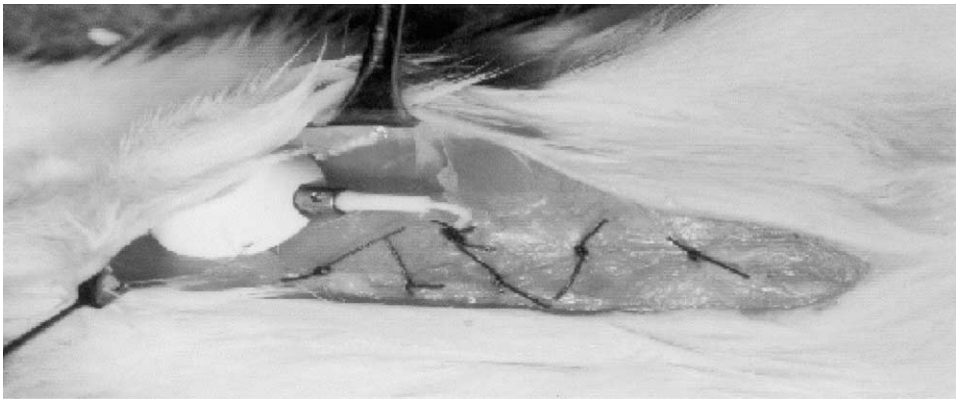

Figure 1. Implantation technique of a s.c. Portsystem for i.p. chemotherapy.

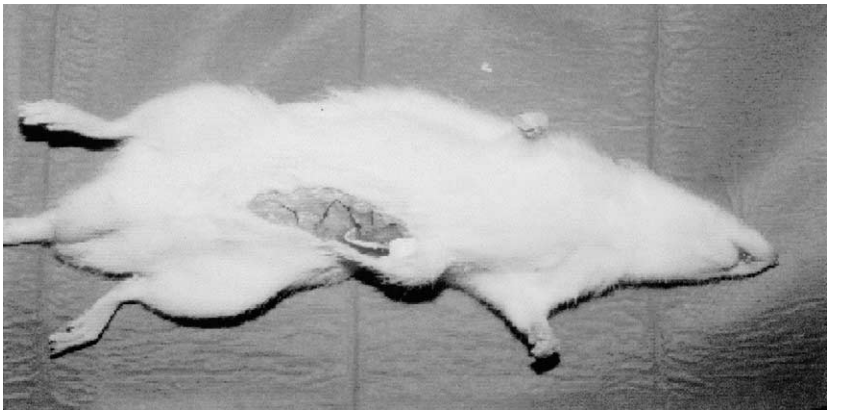

Figure 2. Complete implanted Portsystem.

over the i.p. Portsystem (Figures 1 and 2) on days 15, 20 and 25 after tumor cell implantation. In this group, treatment of an implanted macroscopic peritoneal carcinomatosis was simulated.

Control groups In two control groups, the animals received 5×10^6 tumor cells. In control group I, the animals were killed 30 days after tumor cell implantation and i.p. tumor measurement was performed. This control group (group I/$n = 6$) acted as the control group for the first and second therapy schedule. In control group II ($n = 6$), the animals were killed 15 days after tumor cell implantation. This group was used as control group for the third therapy schedule.

Postoperative examination of tumor growth All animals were kept in individual cages and the presence of side effects (loss of appetite, lethargy, wound infection) to the operation/chemotherapy was assessed twice daily. The animals were sacrificed under general anesthesia on the 30th postoperative day. The animals were autopsied to identify peritoneal carcinomatosis, with qualitative and quantitative determination of metastases. The liver, lungs, small bowel together with the trunk of the mesentery (parietal peritoneum), as well as the greater omentum, were removed and isolated. Toxic reactions on the organs were also noticed. The organ weight was determined on a high-tech digital balance (RD-180-D-xD1; Sartorius, Goettingen, Germany). Using a counter field, the tumor nodules were counted macroscopically on an area measuring $1 \times 1\,cm^2$ in the region of the greater omentum and the parietal peritoneum. Using a conventional histological preparation and H & E staining, all organs and specimens were investigated for evidence of metastatic disease. For each of the animals, at least eight histological sections were obtained. Ascites was collected with a 17-gauge needle near the right and left kidney

Statistical analysis

In every group (I, II and III) the treatment groups (oxaliplatin and CPT-11) were compared against the

control group using the *t*-test (*t*-test/SPSS 9.0. for Windows). Then in groups I, II and III, the CPT-11 and oxaliplatin groups were compared against each other with the *t*-test. A value of $P < 0.05$ was considered to be statistically significant.

Results

Control group I (tumor determination day 30) (Table 2)

All animals developed massive i.p. tumor growth (Figures 3 and 4). Median weight of the greater omentum and mesentery was 4585 and 5261 g. Macroscopic tumor nodules in the greater omentum were 10.5 and in the mesentery 9.00 (median/measuring field $1 \times 1\,cm^2$) (Figures 3 and 5A). Hepatic metastases were found in five animals (Figure 5C). Four animals presented metastases in the lungs (Figure 5D). Microscopic metastases in the pancreas were found in four animals (Figure 5B). The median volume of ascites was 3.0 ml.

Group I (direct intraoperative i.p. chemotherapy) (Table 2)

In group I-B (CPT-11), median weight of the greater omentum and mesentery was 0.87 and 2.64 g and in group I-B was 0.94 and 2.47 g. Macroscopic tumor nodules in the measuring field $1 \times 1\,cm^2$ were in I-A: 0.16 (greater omentum) and 1.16 (mesentery); and in I-B: 1.00 (greater omentum) and 1.33 (mesentery). Histological tumor growth in mesentery and greater omentum was detected in all animals in both groups. Metastases of the liver or lung could not be found. In both groups, no animal presented ascites. In comparison with the control group, all values of both treatment groups were highly significant $p < 0.001$.

Group II (early postoperative i.p. chemotherapy/ days 5, 10 and 15) (Table 3)

Median weight of the greater omentum and mesentery in group II-A (CPT-11) was 1.01 and 2.71 g and in group II-B was 1.11 and 2.93 g. Macroscopic tumor nodules in the greater omentum and in the mesentery in II-A were 0.83 and 1.50 and in II-B were 1.33 and 2.66. Histological examination showed i.p. tumor growth in all animals. No occurrences of liver or lung metastases were found. No animal in either group presented ascites. Significant values were reached when comparing both treatment groups against the control group.

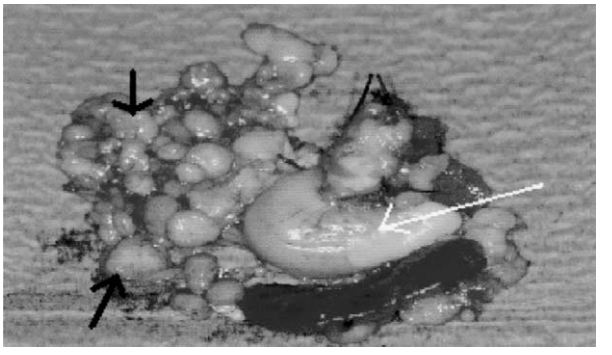

Figure 3. Tumor nodules that have completely invaded the greater omentum 30 days after tumor cell implantation: black arrows, tumor nodules; white arrow, stomach.

Table 2. Results from group I: direct intraoperative chemotherapy

	Group I-A: CPT-11 (300 mg/m^2) $n = 6$	Group I-B: oxaliplatin (60 mg/m^2) $n = 6$	Control group: $n = 6$
Greater omentum	0.87 ± 0.84 g[a]	0.94 ± 0.13 g[a]	4.58 ± 0.55 g
Mesentery	2.64 ± 0.27 g[a]	2.47 ± 0.34 g[a]	5.21 ± 0.60 g
Tumour nodules greater omentum ($1 \times 1\,cm^2$)	0.16 ± 0.75[a]	1.00 ± 0.89[a]	10.5 ± 3.72
Tumor nodules peritoneum ($1 \times 1\,cm^2$)	1.16 ± 0.75[a]	1.33 ± 0.51[a]	9.00 ± 2.89
Hepatic metastases	0	0	5 animals
Pulmo metastases	0	0	4 animals
Ascites	0 ml[a]	0 ml[a]	3.0 ml
Histological tumor detection	all animals in peritoneum+ greater omentum	all animals in peritoneum+ greater omentum	all animals in peritoneum+ greater omentum; 4 animals in pancreas

[a] $p < 0.05$; SPSS *t*-test for Windows.

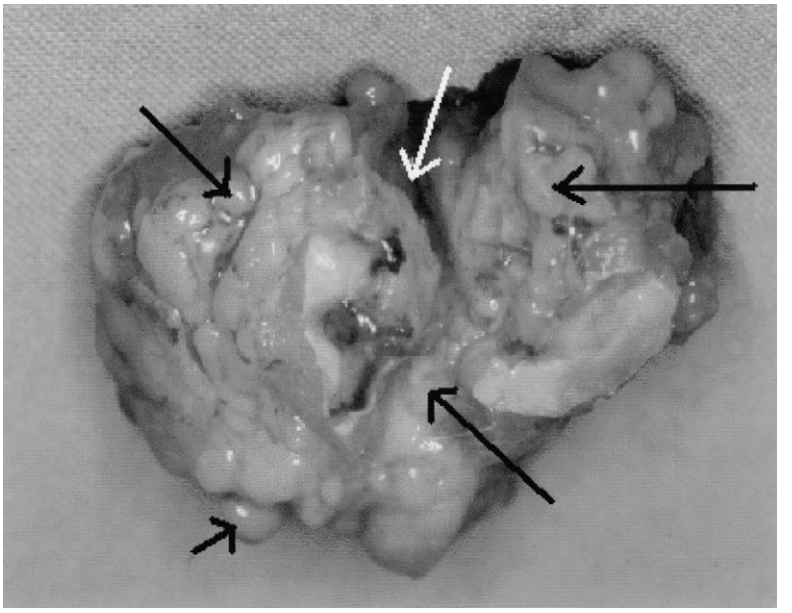

Figure 4. Tumor nodules in the mesentery 30 days after tumor cell implantation: black arrows, tumor nodules; white arrow, a mesenterica superior.

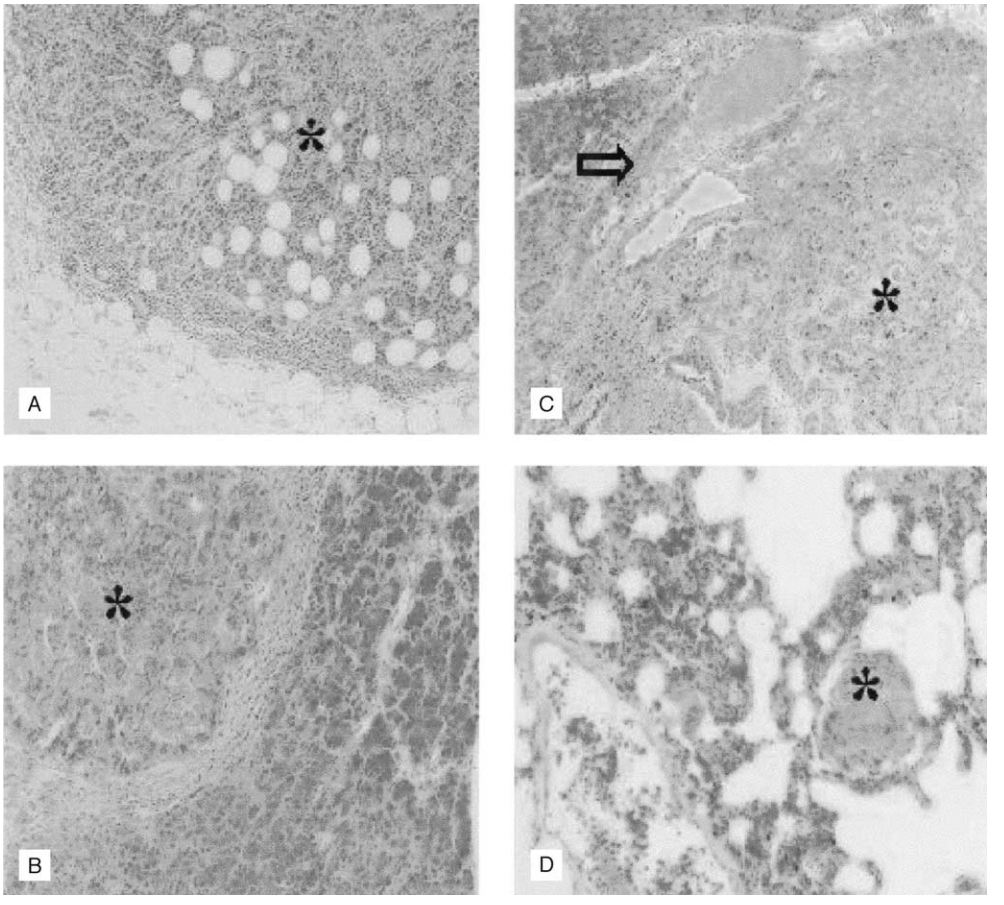

Figure 5. Different organ manifestation of migrating and metastasizing colon carcinoma cells (*) in omentum majus (A; × 100), pancreas (B; × 00), liver (C; × 100) and lung (D; × 400). Invading tumor cells in a blood vessel (arrow).

Table 3. Results group II: early postoperative i.p. chemotherapy (i.p. chemotherapy/days 5,10 and 15)

	Group II-A: CPT-11 (300 mg/m^2) $n = 6$	Group II-B: oxaliplatin (60 mg/m^2) $n = 6$	Control group: $n = 6$
Greater omentum	1.01 ± 0.80 g[a]	1.11 ± 0.99 g[a]	4.58 ± 0.55 g
Mesentery	2.71 ± 0.15 g[a]	2.93 ± 0.11 g[a]	5.21 ± 0.60 g
Tumor nodules greater omentum (1 × 1 cm^2)	0.83 ± 0.75[a]	1.33 ± 0.51[a]	10.5 ± 3.72
Tumor nodules peritoneum (1 × 1 cm^2)	1.50 ± 0.83[a]	2.66 ± 0.81[a]	9.00 ± 2.89
Hepatic metastases	0	1	5 animals
Pulmo metastases	0	0	4 animals
Ascites	0 ml	0 ml	3.0 ml
Histological tumor detection	all animals in peritoneum+ greater omentum	all animals in peritoneum+ greater omentum	all animals in peritoneum+ greater omentum

[a] $p < 0.05$; SPSS *t*-test for Windows.

Table 4. Results group III: treatment of peritoneal carcinomatosis (late postoperative i.p. chemotherapy/days 15, 20 and 25)

	Group III-A: CPT-11 (300 mg/m^2) $n = 6$	Group III-B: oxaliplatin (60 mg/m^2) $n = 6$	Control group: $n = 6$ (day 15)
Greater omentum	3.89 ± 0.27 g	4.13 ± 0.57 g	4.04 ± 0.58 g
Mesentery	3.97 ± 0.16 g	4.19 ± 0.23 g	4.47 ± 0.33 g
Tumor nodules greater omentum (1 × 1 cm^2)	4.83 ± 1.47	5.83 ± 0.75	5.50 ± 1.04
Tumor nodules peritoneum (1 × 1 cm^2)	4.66 ± 1.21	5.33 ± 1.22	5.16 ± 1.32
Hepatic metastases	3 animals	5 animals	1 animal
Pulmo metastases	0 animals	0 animals	0 animals
Ascites	0.33 ml[a]	0.62 ml[a]	1.12 ml
Histological tumor detection	all animals in peritoneum+ greater omentum	all animals in peritoneum+ greater omentum	all animals in peritoneum+ greater omentum

[a] $p < 0.05$; SPSS *t*-test for Windows.

Control group II (tumor determination day 15) (Table 4)

All animals developed i.p. tumor growth. Median weight of the greater omentum and mesentery was 4.04 and 4.47 g. Macroscopic tumor nodules in the greater omentum were 5.5 and in the mesentery were 5.16 (median/measuring field 1 × 1 cm^2). Hepatic metastases were found in one animal. The median volume of ascites was 1.12 ml.

Group III (late postoperative i.p. chemotherapy/days 15, 20 and 25) (Table 4)

In groups III-A (CPT-11) and III-B (oxaliplatin) all animals developed i.p. tumor growth. Macroscopic tumor nodules in group III-A in the greater omentum numbered 4.83 and in the mesentery numbered 4.66 (median/measuring field 1 × 1 cm^2) and in group III-B numbered 5.83 and 5.33. Median weight of the greater omentum and mesentery in group III-A was 3.89 and 3.97 g and in group III-B was 4.13 and 4.19 g. In the oxaliplatin group (III-B) five animals presented liver metastases. Three animals in the CPT-11 showed liver metastases. In group III-A (CPT-11), the median amount of ascites was 0.33 ml. In group III-B the median amount of ascites was 0.62 ml. No metastases of the lungs were detected in both groups. Statistically significant differences between the treatment groups and control group II could not be found.

Side effects

Group I (direct intraoperative i.p. chemotherapy) (Table 5). In both treatment groups, loss of appetite, conjunctivitis and lethargy were observed. In the oxaliplatin group, one animal died as a result of necrotic toxic reactions involving the small intestine and the colon. After 30 days, peritoneal bleedings and necrotic toxic reactions involving the small intestine and colon were detected in another three animals. In the CPT-11 group, after 30 days,

Table 5. Side effects in group I: direct i.p. intraoperative chemotherapy

	Loss of appetite (WHO grade)	Conjunctivitis (WHO grade)	Lethargy (WHO grade)	Death	Wound infection	GI side effects: peritoneal bleeding	GI side effects: toxic necrotic reactions colon, small intestine	Toxic reactions: kidneys
I-A: CPT-11 300 mg/m^2 direct i.p. intraoperative chemotherapy ($n = 6$)	II all animals days 1–15	I–II all animals days 1–8	I all animals days 1–6	0	0	2	0	0
I-B: oxaliplatin 60 mg/m^2 direct i.p. intraoperative chemotherapy ($n = 6$)	II all animals days 1–11	II all animals days 1–20	I all animals days 1–6	1	0	3	2	2

Table 6. Side effects in group II: early postoperative chemotherapy (days 5, 10 and 15)

	Loss of appetite (WHO grade)	Conjunctivitis (WHO grade)	Lethargy (WHO grade)	Death	Wound infection	GI side effects: peritoneal bleeding	GI side effects: toxic necrotic reactions colon, small intestine	Toxic reactions: kidneys
II-A: CPT-11 300 mg/m^2 early i.p. postoperative chemotherapy ($n = 6$)	I–II all animals days 7–25	I all animals days 7–20	I all animals days 7–22	1	1	2	4	0
II-B: oxaliplatin 60 mg/m^2 early i.p. postoperative chemotherapy ($n = 6$)	I–II all animals days 7–24	I–II all animals days 7–22	I–II all animals days 7–22	3	1	4	4	3

Table 7. Side effects in group III: treatment of peritoneal carcinomatosis (days 15, 20 and 25)

	Loss of appetite (WHO grade)	Conjunctivitis (WHO grade)	Lethargy (WHO grade)	Death	Wound infection	GI side effects: peritoneal bleeding	GI side effects: toxic necrotic reactions colon, small intestine	Toxic reactions: kidneys
III-A: CPT-11 300 mg/m^2 late i.p. postoperative chemotherapy ($n = 6$)	III all animals days 16–30	I all animals days 16–30	II–III all animals days 16–30	2	1	2	3	0
III-B: oxaliplatin 60 mg/m^2 late i.p. postoperative chemotherapy ($n = 6$)	III all animals days 16–30	I–II all animals days 16–30	II–III all animals days 16–30	4	3	6	5	4

two animals presented with peritoneal bleeding. No wound infections were detected in either group.

Group II (early postoperative i.p. chemotherapy/ days 5, 10 and 15) (Table 6) After the intermittent chemotherapy all animals presented with minor bleeding in the peritoneum and necrotic toxic reactions involving the small intestine and colon. Three animals in the oxaliplatin group and one animal in the CPT-11 group died as a result of these toxic reactions. Loss of appetite, conjunctivitis and lethargy were the main side effects observed (grade I–II). In both groups, one wound infection was detected.

Group III (late postoperative i.p. chemotherapy/days 15, 20 and 25) (Table 7) In both treatment groups, a high incidence of side effects was observed. Lethargy and loss of appetite approached WHO grade III. All animals needed analgesic medication. In both treatment groups, animals showed peritoneal bleeding and necrotic toxic reactions involving the small intestine colon and kidneys. Two animals in the CPT-11 and four animals in the oxaliplatin group died.

Discussion

In the first therapy schedule of this trial, an intraoperative situation with free cancer cells on the peritoneal surface was simulated. After direct i.p. application of CPT-11 and oxaliplatin it was possible to achieve a highly significant decrease in i.p. tumor growth. No liver metastases occurred in either group. CPT-11 showed a slightly higher effect over oxaliplatin, but it was not statistically significant. Advantages of i.p. CPT-11 application were reported following a pharmacokinetic and efficacy experimental study by Guichard *et al.*[29] The study group found that i.p. administration of CPT-11 was more efficient and less toxic than i.v. administration to mice bearing C26 colon cancer. This trial deals with survival time; after i.p. administration of 100 mg/kg, survival time of the mice was the same as that observed after 300 mg/kg given i.v. In our trial, after direct intraoperative i.p chemotherapy with CPT-11, animals showed a significantly lower number of tumor nodules in the omentum and mesentery, and less ascites than animals in the control group. Another important point is that only one rat treated with i.p. CPT-11 died as a result of side effects.

Following direct intraoperative i.p. administration of oxaliplatin, animals presented fewer tumor nodules in the peritoneum and less ascites than animals in the control group. However, two animals died as a result of toxic side effects. Los *et al.*[30] demonstrated a high i.p. effect of oxaliplatin against CC531.RL4 tumor cells in their experimental trial. This is a cisplatin-resistant cell line that may point to some value for oxaliplatin in treating ovarian cancer patients who do not respond to previous cisplatin treatment.

In the second therapy schedule, the aim was to simulate early postoperative chemotherapy. In all animals, an i.p. Portsystem was implanted, so it was always possible to administer chemotherapy in a consistent manner into the peritoneal cavity. Both cytostatic drugs brought about a statistically significant decrease in i.p. tumor spread. However, CPT-11 appeared to show benefits over oxaliplatin. Following the intermittent application of oxaliplatin, four animals died as a result of toxic reactions of the colon, showing ileus symptoms and peritoneal inflammation Also, two animals in the oxaliplatin group developed superficial liver metastases.

In two other experimental trials, peritoneal carcinomatosis was reduced after intermittent i.p. chemotherapy. In a peritoneal tumor nude mice model, Maruyama *et al.*[31] compared the effect of sequential i.p. against i.v. administration of MTX/5-FU. In this trial, the i.p. application of MTX/5-FU produced a statistically significantly greater decrease in i.p. tumor growth than that shown after i.v. application. Using the matrix metalloproteinase inhibitor Batimastat, a French working group significantly prolonged survival in tumor-bearing rats after postoperative sequential i.p. administration.[32] In this experimental trial the highest effect in terms of decreasing i.p. tumor growth was reached after early (2 days after tumor cell implantation) i.p. chemotherapy. Later application (13 days after tumor cell inoculation) of Batimastat reduced peritoneal and liver metastasis, but this was not so efficient as that observed after early i.p. administration. These results correlate approximately with the results we found in our trial.

In our third therapy schedule, we set out to investigate the value of i.p. chemotherapy in reducing a manifest peritoneal carcinomatosis. The results revealed that neither cytostatic drug produced any significant reduction in the i.p. tumor growth. However, two benefits were observed in the treatment groups; the extreme high i.p. tumor growth and ascites volume that animals in control group I presented was not achieved in the treated animals. In the CPT-11 group, liver metastases did not occur in 50% of the cases. The high incidence of side effects

revealed in this treatment group (two animals in the CPT-11 group and four animals in the oxaliplatin group died) may be a consequence of peritoneal tumor growth and i.p. chemotherapy.

The problem of treating a peritoneal carcinomatosis with visible nodules is that it is not possible for cytostatic agents to diffuse completely through the tumor nodules and reach their center. This problem has been described by Shiu and Fortner.[33] The authors used a hyperthermic i.p. treatment concept in implanted peritoneal cancer in rats. It was possible to cure 58% of the rats by direct intraoperative and early postoperative i.p. hyperthermic treatment. The method, however, was ineffective against macroscopic tumor nodules. The authors considered that a therapeutic temperature was not achieved in the center of the tumor nodules. It is important to point out that in this trial nearly 30% of the heat-treated rats died during or 24 h after treatment. Treatment of an existing peritoneal carcinomatosis was reported by a French working group.[34] Following experimentally induced peritoneal carcinomatosis in BDXI rats, peritoneal and omental tumors were resected after 20 days. One animal group received cisplatin in combination with epinephrine i.p.; the other group underwent only the surgical procedure. The survival rate in the combination group treated with the i.p. combination was considerably greater, but a healing of peritoneal carcinomatosis could also not be achieved.

Conclusion

Under experimental conditions CPT-11 and oxaliplatin were shown to be highly effective in reducing i.p. tumor spread after direct i.p. intraoperative application. A beneficial effect of i.p. administration of CPT-11 or oxaliplatin to decrease i.p. tumor growth was also noticed after early i.p. chemotherapy. CPT-11 was a little more effective and with lower side effects than oxaliplatin, but the differences were not statistically significant. We cannot say that our trial is the key to solving the problem of the high rate of peritoneal carcinomatosis and local recurrence in colon carcinoma. The small number of rats employed in the experiment cannot provide a sufficient basis for a general call for changes in adjuvant treatment of colorectal carcinoma. Certainly, it will not be possible to extrapolate these results obtained from rodents to humans. However, the high incidence of side effects observed for oxaliplatin in intermittent i.p. chemotherapy cannot be completely ignored. This trial will help to close the existing gaps in experimental data and will be a useful addition to studies into the use of i.p. chemotherapy for the prevention of peritoneal carcinomatosis. The results have clearly shown that it was not possible to treat a manifest peritoneal carcinomatosis in this way. Intraperitoneal chemotherapy initiated on the 15th postoperative day was only capable of reducing (not statistically significant) the i.p. tumor spread. Most authors reporting on similar experimental investigations have described similar results.[28–34] Further trials using combinations of other cytostatic agents along with new drugs (MMP inhibitors, angiogenesis inhibitors) need to be performed.

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