HIPEC treatment of peritoneal carcinomatosis in colorectal and gastric cancer

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CHAPTER 10

Treatment of peritoneal dissemination in stomach cancer patients with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC): Rationale and design of the PERISCOPE-study

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Abstract

Background
The main objectives of this study are (I) to investigate the safety, tolerability and feasibility of gastrectomy combined with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) after neoadjuvant systemic chemotherapy, as a primary treatment option for advanced gastric cancer with tumor positive peritoneal cytology (C+) and/or limited peritoneal (P+) carcinomatosis and (II) to determine the maximum tolerated dose of intraperitoneal docetaxel in combination with a fixed dose regimen oxaliplatin in this treatment schedule.

Methods
The study is a multicenter, open label, dose-escalation combined phase I-II study, enrolling 20-30 patients meeting the inclusion criteria, using a 3+3 escalation design. All patients with locally advanced gastric adenocarcinoma and positive peritoneal cytology or limited peritoneal carcinomatosis, assessed with diagnostic laparoscopy, following neoadjuvant chemotherapy are eligible for inclusion. At laparotomy cytoreductive surgery (CRS) and a total or partial gastrectomy with a D2 lymph node dissection is performed. An open HIPEC technique is used with oxaliplatin for 30 minutes and a dose-escalation will be performed with 0-50-75-100-125-150 mg/m^2 of docetaxel for 90 minutes. The primary endpoint in this study is treatment related toxicity graded according to the NCI Common Toxicity Criteria version 4.0.

Discussion
The PERISCOPE study will determine the safety, tolerability and feasibility of gastrectomy combined with CRS + HIPEC using oxaliplatin in combination with docetaxel after neoadjuvant systemic chemotherapy as a primary treatment option for patients with advanced gastric cancer with tumor positive peritoneal cytology and/or limited peritoneal carcinomatosis. The study will provide pharmacokinetic data on the intraperitoneal administration of both oxaliplatin and docetaxel. The data acquired in the study are a prerequisite for the safe conduct of future studies of HIPEC in gastric cancer patients either in the prophylactic or therapeutic setting.
Background

Patients with advanced gastric cancer have a poor prognosis, resulting in a 5-year survival rate of 20-30 percent, even after potentially curative surgery. Approximately 15% of patients have manifest synchronous peritoneal involvement at diagnosis. Patients with gastric cancer and peritoneal carcinomatosis, either synchronous or metachronous as manifestation of recurrent disease, have a poor prognosis with a median survival of about 3 months without treatment. It has been proposed that extended resection, consisting of gastrectomy and peritonectomy, combined with the administration of intraperitoneal chemotherapy might improve survival in patients with peritoneal carcinomatosis from gastric cancer. The rationale of administering chemotherapeutic agents into the peritoneal cavity is based on the peritoneal plasma barrier. The limited permeability of the peritoneum allows the delivery of high concentration of chemotherapeutic drugs directly into the peritoneal cavity without the danger of corresponding high concentrations in plasma with the subsequent systemic reactions.

Intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) has an established role in the treatment of peritoneal carcinomatosis from colorectal cancer, appendiceal cancer and pseudomyxoma peritonei. The role of HIPEC in the treatment of gastric cancer with peritoneal carcinomatosis is uncertain. A recent systematic review showed in the better designed studies an improved survival in patients receiving intraperitoneal chemotherapy and cytoreductive surgery compared to patients having surgery alone. Overall, good quality evidence is limited as many studies include heterogeneous patient populations and differ in type, timing, method and duration of drug delivery. Currently, various intraperitoneal chemotherapeutic drugs are used in gastric cancer but the best and the most suitable regime is unknown. An important issue which needs therefore to be addressed is the choice of neoadjuvant and intraperitoneal chemotherapy and the most effective dosing scheme.

In the current manuscript, we describe a study protocol aimed to evaluate the safety, tolerability and feasibility of gastrectomy combined with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with oxaliplatin and docetaxel, following neoadjuvant systemic chemotherapy, as primary treatment for advanced gastric cancer with tumor positive peritoneal cytology (C+) or limited peritoneal carcinomatosis (P+).
Methods/Design

Hypothesis
The design of the current study is based on the beneficial effects of HIPEC in various gastrointestinal malignancies. Gastric cancer, with its frequent peritoneal and locoregional recurrence, theoretically seems a suitable disease for HIPEC treatment. We hypothesized that CRS + HIPEC, after neoadjuvant chemotherapy, will be a safe and beneficial treatment in selected gastric cancer patients, with minimal peritoneal dissemination or positive tumor cytology.

Objectives
The main objectives of this study are (I) to investigate the safety, tolerability and feasibility of gastrectomy combined with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) after neoadjuvant systemic chemotherapy, as a primary treatment option for advanced gastric cancer with tumor positive peritoneal cytology (C+) and/or limited peritoneal (P+) carcinomatosis and (II) to determine the maximum tolerated dose of intraperitoneal docetaxel in combination with a fixed dose regimen oxaliplatin in this treatment schedule. We furthermore aim to investigate (a) the pharmacokinetics of intraoperative hyperthermic intraperitoneal oxaliplatin and docetaxel and (b) to determine the two-year disease-free and overall survival of advanced gastric cancer patients with tumor positive peritoneal cytology and/or limited peritoneal carcinomatosis treated with this treatment schedule.

Design
The study is a multicenter, open label, dose-escalation combined phase I-II study, enrolling 20-30 patients meeting the inclusion criteria, using a 3+3 escalation design. At first, up to three patients will be treated with at the lowest docetaxel dose level. If none of the patients treated in a single dose cohort experiences a dose-limiting toxicity, the next three patients can be treated at a higher dose level. If one of three patients in the same dosage cohort experiences a dose-limiting toxicity, a total of six patients will be treated at the same dose level. When dose-limiting toxicities occur in two or more patients in a cohort of at least three patients, no further dose escalation steps will be undertaken. The maximum tolerated dose is defined as the dose below the dose-level that causes dose-limiting toxicity in two or more patients in a cohort of at least three patients.
Study procedures

All patients with locally advanced (T3-T4, any N) gastric adenocarcinoma and positive peritoneal cytology (C+) or limited peritoneal carcinomatosis (P+), assessed with diagnostic laparoscopy, following neo-adjuvant chemotherapy and no evidence of distant metastasis, are eligible for inclusion. Following informed consent, patients meeting inclusion criteria will be scheduled for surgery combined with HIPEC. At laparotomy, the presence and extent of peritoneal tumor deposits will be recorded. When a potentially radical resection of the primary tumor can be achieved, a total or partial gastrectomy with a D2 lymph node dissection is performed. In patients with limited peritoneal carcinomatosis, cytoreductive surgery (CRS), as described earlier, is done with the objective to leave no macroscopic tumor behind. Intraperitoneal chemoperfusion is performed using an open HIPEC technique. At an intraperitoneal temperature of 41-42 °C, 460 mg/m² oxaliplatin is added to the perfusate. After 30 minutes, the perfusion fluid is drained from the abdomen. In successive patients a dose-escalation study will be performed perfusing the peritoneal cavity with 0-50-75-100-125-150 mg/m² docetaxel for 90 minutes at 37 °C. The flow chart of this study is depicted in Figure 1. For pharmacokinetic analysis, plasma and perfusion samples will be obtained at the start, after 15 minutes and at end of oxaliplatin perfusion and at the start of docetaxel perfusion, after 45 minutes and at the end of docetaxel perfusion. Approximately 2 and 12 hours after completion of the perfusion plasma samples will be collected.

Endpoints

The primary endpoint in this study is treatment related toxicity graded according to the NCI Common Toxicity Criteria version 4.0. The endpoint will determine the maximum tolerated dose of intraperitoneal docetaxel in combination with a fixed dose of oxaliplatin. Secondary endpoints in this study are postoperative morbidity and mortality, pharmacokinetic parameters, cytoreductive completeness score, patterns of tumor recurrence and disease-free and overall survival.
Figure 1, study flow chart

Study population

Patients meeting the following inclusion criteria will be enrolled into the study: patients with a biopsy proven adenocarcinoma of the stomach, T3-T4 tumor based upon CT-scan and/or EUS results, with tumor positive peritoneal cytology and/or peritoneal carcinomatosis limited to the upper abdominal cavity, i.e., above the transverse colon, and/or at the most at one location in the lower abdominal cavity confirmed by diagnostic laparoscopy. Patients have to be treated with neoadjuvant chemotherapy, with the last course ending within 8 weeks prior to exclusion. Accepted neoadjuvant chemotherapy regimens generally consist of a platinum-drug combined with a fluoropyrimidine. Additionally, an anthracycline or taxane may have been added according to local protocol. Examples of accepted chemotherapy regimens are: docetaxel + oxaliplatin + capecitabine (DOC), docetaxel + cisplatin + 5-FU (DCF), epirubicin + cisplatin + capecitabine (ECC), epirubicin + oxaliplatin + capecitabine (EOC). Patients have to be older than 18 years, with acceptable performance status and adequate bone marrow, hepatic and renal function. Patients with a life expectancy shorter than 3 months, patients with known distant metastases, small bowel dissemination, or signs of local irresectability will be excluded. Patients with recurrent gastric cancer, prior treatment of gastric cancer with systemic anticancer therapy or metachronous peritoneal carcinomatosis will not be eligible for the current trial. Furthermore, progressive disease on neoadjuvant chemotherapy precludes
inclusion. Patients who are pregnant, breast feeding or have an active pregnancy ambition will be excluded. Lastly, patients with known hypersensitivity for any of the applied chemotherapeutic agents and/or their solvents, uncontrolled infectious disease, known history of Human Immunodeficiency Virus HIV-1 or HIV-2 type, hepatitis B or C with active viral replication, recent myocardial infarction (< 6 months) or unstable angina, uncontrolled diabetes mellitus or any medical condition not yet specified above that is considered to possibly, probably or definitely interfere with study procedures will be excluded from this study. Table 1 provides an overview of all inclusion and exclusion criteria. In total approximately 20-30 patients will be included in the current study; however this number is highly dependent on the number of dose-escalations.

Table 1. In- and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>- Biopsy proven adenocarcinoma of the stomach (including tumors at the esophagogastric junction provided that the bulk of the tumor is located in the stomach for which the intended surgical treatment is a gastric resection, and not a resection of the esophagus and cardia)</td>
</tr>
<tr>
<td>- T3-T4 tumor based upon CT-scan and/or EUS results</td>
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<tr>
<td>- Treated with neoadjuvant systemic chemotherapy with the last course ending within 8 weeks prior to inclusion</td>
</tr>
<tr>
<td>- Tumor positive peritoneal cytology and/or peritoneal carcinomatosis limited to the upper abdominal cavity (above the transverse colon) and/or at the most at one location in the lower abdominal cavity (e.g., Douglas’ pouch, ovarian metastasis, Sister Mary Joseph nodule) confirmed by diagnostic laparoscopy or laparotomy</td>
</tr>
<tr>
<td>- Age ≥ 18 years</td>
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<td>- WHO performance status 0-1</td>
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<td>- ASA classification I-III</td>
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<tr>
<td>- Adequate bone marrow, hepatic and renal function, i.e., minimal acceptable laboratory values at start of the study inclusion:</td>
</tr>
<tr>
<td>a. ANC ≥ 1.5 x 10^9/L</td>
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<tr>
<td>b. Platelet count ≥ 100 x 10^9/L</td>
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<tr>
<td>c. Serum bilirubin ≤ 1.5 x ULN, and ALAT and ASAT ≤ 2.5 x ULN</td>
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<tr>
<td>d. Creatinine clearance ≥ 50 ml/min (measured or calculated by Cockcroft-Gault formula).</td>
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<tr>
<td>- Negative pregnancy test (urine/serum) for female patients of childbearing potential</td>
</tr>
<tr>
<td>- Life expectancy ≥ 3 months, allowing adequate follow-up</td>
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<tr>
<td>- Able and willing to undergo blood sampling for pharmacokinetics</td>
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<tr>
<td>- Written informed consent</td>
</tr>
</tbody>
</table>
Exclusion criteria

- Distant metastases (e.g., liver, lung, para-aortic lymph nodes) or small bowel dissemination
- Signs of local irresectability
- Recurrent gastric cancer
- Metachronous peritoneal carcinomatosis
- Prior resection of the primary gastric tumor
- Pregnancy, breast feeding or active pregnancy ambition
- Unreliable contraceptive methods. Patients enrolled in this study must agree to use a reliable contraceptive method throughout the study
- Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type
- A known history of hepatitis B or C with active viral replication
- Recent myocardial infarction (< 6 months) or unstable angina
- Uncontrolled diabetes mellitus
- Any medical condition not yet specified above that is considered to possibly, probably or definitely interfere with study procedures, including adequate follow-up and compliance and/or would jeopardize safe treatment
- Known hypersensitivity for any of the applied chemotherapeutic agents and/or their solvents

Ethics and safety

After extensive explanation of the study objectives and procedures, written informed consent will be obtained in all patients. The study protocol has been approved by the medical ethical committee of the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital. The study will be performed in accordance with the declaration of Helsinki. The protocol of this study is registered at the Netherlands Trial Registration with code NTR4250. A waiting period of 4 weeks will be observed between the HIPEC procedures in subsequent patients to allow an adequate assessment of toxicity and adverse events in individual patients before the next patient will be treated with a higher dose of docetaxel. At completion of a cohort of three patients in one dose-level, the study team will discuss the toxicity and morbidity in the patients of the cohort and will decide in consensus whether dose-escalation can be performed or whether the endpoint of the study has been reached.

Discussion

Rationale of the study

The current study aims to determine the safety, tolerability and feasibility of gastrectomy combined with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy
(HIPEC) using oxaliplatin in combination with docetaxel after neoadjuvant systemic chemotherapy, as a primary treatment option for patients with advanced gastric cancer with tumor positive peritoneal cytology and/or limited peritoneal carcinomatosis. The current systematic reviews and randomized trials of intraperitoneal chemotherapy in gastric cancer patients, all suggest that intraperitoneal chemotherapy may be beneficial in selected patients.\textsuperscript{7,9-11} However, many of these studies in gastric cancer are of limited quality as they are frequently based on heterogeneous patient populations including either patients at risk being treated prophylactic or patients with manifest peritonitis treated with therapeutic intent. Most studies use different (neo) adjuvant and intraperitoneal chemotherapy regimens, and many of these studies have been performed in Asiatic countries which raises the question whether the results can be extrapolated to other ethnic populations.

Well-designed prospective randomized trials are warranted with clearly defined inclusion criteria, with distinct neoadjuvant and adjuvant treatment protocols and with a uniform surgical and HIPEC treatment. Prior to such trials pharmacokinetic studies are mandatory to identify the most optimal chemotherapeutic regimen to be compared to the best available standard treatment. An important issue in intraperitoneal chemotherapy in gastric cancer therefore is the choice and dosing of the chemotherapeutic agent. The present PERISCOPE study was designed as the first dose escalation trial of intraperitoneal docetaxel in gastric cancer.

**Choice of intraperitoneal drugs**

Several regimens of intraoperative hyperthermic chemoperfusion in gastric cancer have been explored or are still under investigation.\textsuperscript{7} Mitomycin and cisplatin are the most frequently used chemotherapeutic agents, originating from the widespread usage of these drugs in ovarian and colorectal HIPEC. We performed an extensive literature review on the selection of intraperitoneal chemotherapy for the use in patients with gastric cancer.\textsuperscript{12} Theoretically, a combination of drugs will results in a more effective treatment. Based on a pioneer study of Elias et al. oxaliplatin is increasingly used as a drug for intraperitoneal chemotherapy with promising results.\textsuperscript{13} Oxaliplatin was preferred over cisplatin, as oxaliplatin is not nephrotoxic and appears to have a more favorable pharmacokinetic profile. Following the study of Elias et al., the current dosage of intraperitoneal oxaliplatin is known and widely applied, which provides a valuable starting point for further exploration of combinations of intraperitoneal chemotherapeutic drugs.
The taxanes, docetaxel and paclitaxel, both seem promising drugs for intraperitoneal chemotherapy, as there systemic uptake is limited, permitting the use of high local concentrations. As the tumor- and cell penetration appears to significantly higher in docetaxel compared to paclitaxel following intraperitoneal administration, we selected docetaxel as taxane.\textsuperscript{14} Additionally, severe anaphylactoid hypersensitivity reactions have been described of paclitaxel’s solvent Cremophor EL.\textsuperscript{15} A combination of oxaliplatin and docetaxel may result in a promising chemotherapeutic regimen. However, no dose-finding study has been performed on intraperitoneal intraoperative docetaxel administration.

Furthermore, the intraperitoneal administration of the combination of oxaliplatin and docetaxel has not yet been investigated.

**Patient selection**

For this study we have chosen a subgroup of gastric cancer patients, those with limited peritoneal carcinomatosis or with positive peritoneal cytology, in which based on the current literature CRS + HIPEC might improve the overall and disease free survival. It was therefore considered ethically justified to perform a study in this selected patient group. Patients with extensive disease or unresectable distant metastases were excluded, as the prognosis of these patients is extremely poor, and these patients qualify for palliative treatment or best supportive care only and are not eligible for an extensive treatment of which the associated complications do not outweigh the potential benefits. In patients with limited peritoneal dissemination though a complete (R0) cytoreduction can be achieved which is mandatory as complete cytoreduction is one of the key factors associated with improved survival following HIPEC treatment.\textsuperscript{16,17} Patients with tumor positive cytology of the peritoneal fluid without macroscopic peritoneal carcinomatosis have a median survival of 15 months and a five-year survival rate of 0\%\textsuperscript{18} As many as 15\% of patients without visible metastatic disease will have tumor positive peritoneal cytology, and this proportion will increase to 30-50\% in patients with serosa-infiltrating tumors or lymph node metastases.\textsuperscript{19-21} In these high risk patients HIPEC is expected to decrease the risk of peritoneal dissemination and for this reason this group of patients was included in the study.

Staging laparoscopy is a mandatory investigation in the study and in the diagnostic work-up of patients with gastric cancer. It allows the evaluation of the presence or absence of peritoneal metastases and allows the sampling of peritoneal cytology fluid and may prevent futile surgical exploration in up to 30\% of patients.\textsuperscript{22}
Neoadjuvant chemotherapy

Adjuvant therapies, such as perioperative chemotherapy and postoperative chemoradiotherapy, have demonstrated an improved progression-free and overall survival in patients with resectable adenocarcinoma of the stomach. Commonly applied regimes include epirubicin + cisplatin + continuous 5-fluorouracil (5-FU) (ECF), epirubicin + cisplatin + capecitabine (ECC), and docetaxel + cisplatin + 5-FU (DCF). Similarly, these regimens are used in the palliative setting for metastatic gastric cancer. All three regimens have fairly good response rates of 35 – 50%, but the median survival will only be prolonged with a few months and does not surpass 12 months. Neoadjuvant chemotherapy at present is considered standard treatment in surgery with curative intent for gastric cancer. In the current study it was decided that patients prior to inclusion have to be treated with at least one course of neoadjuvant systemic chemotherapy. All presently used neoadjuvant chemotherapy regimens i.e. those consisting of a platinum-drug combined with a fluoropyrimidine, or those with an additional anthracycline or taxane according to the local protocol were included. Patients showing progression under neoadjuvant chemotherapy were excluded for the study.

Conclusion

The PERISCOPE study will determine the safety, tolerability and feasibility of gastrectomy combined with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) using oxaliplatin in combination with docetaxel after neoadjuvant systemic chemotherapy as a primary treatment option for patients with advanced gastric cancer with tumor positive peritoneal cytology and/or limited peritoneal carcinomatosis. The study will provide pharmacokinetic data on the intraperitoneal administration of both oxaliplatin and docetaxel. The data acquired in the study are a prerequisite for the safe conduct of future studies of HIPEC in gastric cancer patients either in the prophylactic or therapeutic setting. The ultimate goal of this study is to establish a new treatment standard for advanced gastric cancer patients by providing significant survival benefit with acceptable treatment related morbidity.
References

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