

**Clinical pharmacology of platinum-based
hyperthermic intraperitoneal chemotherapy:
the impact of flushing on tumor, systemic and
personnel exposure
(GUTOX)**

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Version 2

**Clinical pharmacology of platinum-based hyperthermic intraperitoneal chemotherapy:
the impact of flushing on tumour, systemic and personnel exposure**

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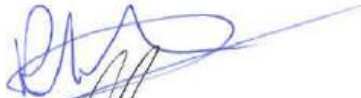
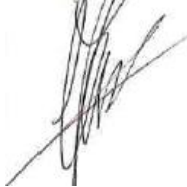

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AAS	Flameless atomic absorption spectrometry
AE	Adverse Event
ALT	Alanine transaminase
AR	Adverse reaction
AST	Aspartate transaminase
AUC	Area Under the Curve
C _{max}	Maximum observed plasma concentration after single dose administration
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
HIPEC	hyperthermic intraperitoneal chemotherapy
IEC	Independent Ethics Committee
ICP-OES	inductively coupled plasma optical emission spectrometry
IPCH	intra-operative intra-peritoneal chemo-hyperthermia
L	Liter
LDH	Lactate Dehydrogenase
MDRD	Modified Diet in Renal Disease
METC	Medical research ethics committee (in Dutch: Medisch Ethische Toetsing Commissie)
PC	peritoneal carcinomatosis
PI	Principal Investigator: a person responsible for the conduct of a clinical study at a study site. Every study centre has a principal investigator.
PK	Pharmacokinetics
Pt	Platinum
PUF	plasma ultrafiltrate
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party
SUSAR	Suspected Unexpected Serious Adverse Reaction
T _{1/2}	Half life time
T _{max}	Time to maximum observed plasma concentration after dose
UAR	Unexpected Adverse Reaction
UMCN	Radboud University Medical Center (in Dutch: Radboudumc)
WHO	World Health Organization
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is standard care in the treatment of patients with peritoneal carcinomatosis as a result of intra-abdominal cancers. Cytoreduction is a procedure that aims for the complete removal of all visible tumours affecting the protective lining of the abdomen. The cytoreductive procedure itself is complex and can last several hours. After the surgical procedure is completed, HIPEC is performed to attack non-visible tumour cells. The main goal of HIPEC is to obtain high local concentrations of the drug in the abdominal cavity with high penetration in tumour tissue, while avoiding systemic exposure. In many (inter)national centres oxaliplatin is used for the primary HIPEC treatment. The recommended dose of oxaliplatin is 460 mg/m^2 perfused for 30 minutes at 43°C in dextrose 5%, performed following the open 'coliseum' technique. This includes lifting the edges of the surgical wound upwards and suspending them under traction by threads, thus optimizing exposure of intra-abdominal viscera. The abdomen is filled with dextrose 5% and with a rollerpump the perfusate is circulated in the abdominal cavity. Although the oxaliplatin dose of 460 mg/m^2 is widely accepted, the exact procedure of HIPEC differs between institutions and surgeons. Platinum concentration in the perfusate at the beginning of HIPEC depends on both body surface area and the volume of the abdominal cavity. Due to a great variety in the volume of the abdominal cavity, platinum concentration in the perfusate might differ between patients. Moreover, there is no consensus about the usefulness of flushing the HIPEC system with crystalloids at the end of oxaliplatin administration. Flushing is predominantly performed with the idea to minimize both systemic exposure of ultrafilterable platinum and personnel exposure to platinum-contaminated exudate. On the other hand, HIPEC without flushing might increase effectiveness because intraperitoneal tumour cells are exposed to high concentrations of oxaliplatin for a longer time period. The option of flushing is based on an individual preference of the surgeon. Currently, there is a lack of knowledge on the effect of flushing on tumour platinum exposure, systemic platinum exposure and platinum concentration in drain exudate and thereby personal exposure. Therefore we want to perform a study to investigate the effect of flushing after HIPEC on tumour exposure, systemic exposure and on wound exudate concentration. The results of this study will provide answers about the effect of flushing the abdominal cavity after HIPEC procedure. If flushing has no effect on peritoneal tissue exposure but does decrease systemic exposure and/or platinum concentration in exudate, flushing should be recommended to decrease personnel exposure and systemic toxicity.

Objective

Primary objective:

1. To determine the effect of flushing after HIPEC on tissue platinum exposure

Secondary objectives:

1. To explore the effect of flushing after HIPEC on wound exudate platinum concentration
2. To explore the effect of flushing after HIPEC on systemic exposure of total and unbound platinum

3. To explore the relation between the platinum concentration in instillate on tissue platinum exposure
4. To explore the relation between the platinum concentration in instillate on systemic exposure of total and unbound platinum exposure
5. To explore the effect of the degree of cyto-reduction on systemic total and unbound platinum exposure

Study design

Single-centre, prospective, open, pharmacokinetic (PK) cohort study.

Study population

Twenty patients with peritoneal carcinomatosis as a result of intra-abdominal cancers who are already planned for HIPEC treatment with oxaliplatin as part of routine clinical care will be included in the study.

Intervention

The first 10 patients will undergo HIPEC procedure with flushing afterwards (the current practice by Radboudumc), followed by 10 patients who will be treated with HIPEC without flushing afterwards (new Radboudumc protocol that will be implemented in the beginning of 2018). Peritoneal fluid, peritoneal tissue, blood and wound exudate samples will be collected in all patients on prespecified time points during and after the HIPEC procedure.

Main study parameters/endpoints:

The main study parameter is the change in tissue platinum exposure before and after flushing. Tissue platinum exposure is expressed in concentration platinum per milligram tissue (ng/mg).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Patients who participate in the study will receive the standard treatment. Therefore, the risk for participation in this study is regarded negligible. Collection of peritoneal fluid, blood, and wound exudate samples do not put patients at risk or interfere with standard treatment. Three 5ml peritoneal fluid samples will be taken 10, 20 and 30 minutes after intraperitoneal administration of oxaliplatin. Wound exudate samples of 5 ml will be taken from drain bottles at the moment that they are changed until day three post-surgery. During and after HIPEC a total of thirteen blood samples of 10ml will be taken from a central venous catheter that is placed as routine care prior to cytoreductive surgery with HIPEC. In the group of patients receiving HIPEC with flushing two 5-cm diameter non-tumour peritoneal tissue samples will be taken prior to and at the end of flushing. In the group of patients receiving HIPEC without flushing one 5-cm diameter non-tumour peritoneal tissue sample will be taken prior to abdominal closure. Compared to the complexity and amount of cytoreduction that is performed during surgery this can be considered as a negligible additional tissue collection procedure.

Benefits associated with participating in this study are that patients and their treating physician get insight into the effect of flushing after HIPEC on tumour platinum exposure and that the HIPEC procedure can be optimized for future patients.

1. INTRODUCTION AND RATIONALE

Peritoneal carcinomatosis is generally considered to be an untreatable terminal disease with a median survival of 6 months with 5-FU-based chemotherapy(1) and 1 year with chemotherapy including oxaliplatin. Systemic chemotherapy provides limited benefit. The use of cytoreductive surgery followed by HIPEC for peritoneal carcinomatosis as a result of intra-abdominal cancers has shown great improvement of survival rates compared with standard palliative surgery and chemotherapy. Survival rates improved to a median of two years and 20% of patients live longer than five years after the treatment (2-6). Therefore cytoreductive surgery combined with HIPEC in the treatment of peritoneal carcinomatosis is progressing towards a new standard of care (7). Despite the success of the treatment, there is a lack of agreement on many issues concerning the cytotoxic drug, dose, duration, carrier solution and technique.

Although no comparative studies between different cytotoxic drugs have been performed, the experience that has been obtained with oxaliplatin is most encouraging. Therefore primary HIPEC procedure consists of intraperitoneal administration of oxaliplatin. The main goal of HIPEC is to obtain high local oxaliplatin concentrations in the abdominal cavity with high penetration in tumour tissue, while avoiding systemic exposure. The advantage of intraperitoneal administration is confirmed in several PK studies (8, 9). Administration of 5-FU significantly increases the antitumor activity of intravenous administered oxaliplatin in the treatment of colorectal cancer (10-12). HIPEC with oxaliplatin is preceded by intravenous administration of 5-fluorouracil (400-450 mg/m²) and folic acid (20 mg/m²), to potentiate oxaliplatin efficacy in the tumour cells (9). 5-FU is distributed to peritoneal fluid and tumor nodules after intravenous administration during HIPEC (13).

In order to balance cytotoxic activity and risk of toxicity, which is related to systemic exposure, it is important to study the PK of oxaliplatin during the HIPEC procedure. Based on previous PK work the most efficient dose for administration of oxaliplatin during HIPEC has been defined (8, 9, 14-27). The recommended dose of oxaliplatin is 460 mg/m² perfused during 30 minutes at 43°C in dextrose 5% following the open 'coliseum' technique. The open 'coliseum' technique is chosen because previous experimental data suggest higher tissue penetration and a more homogenous distribution compared to the closed technique (28). Some studies suggest the use of a standard volume of instillate of 2 L/m², leading to a fixed concentration of oxaliplatin in the peritoneal cavity (9). In the Radboud University Medical Centre the abdominal cavity of the patient is completely filled with dextrose 5% before oxaliplatin is administered, to ensure contact with the whole peritoneum, for which a volume up to 6 litres may be needed. Because the volume of the abdominal cavity differs largely between patients, there is a great variety of oxaliplatin concentration in the instillate and thereby in the abdominal cavity. Together with the duration of the procedure, oxaliplatin concentration in instillate is an important variable that might influence tumour penetration and systemic absorption (9, 16, 21). In addition to these variables tumour penetration can be influenced by several other pharmacokinetic and non-pharmacokinetic variables, including carrier solution, pressure, tumor nodule size, nodule density, vascularity and interstitial fluid pressure.

Although a national standardized drug dose for oxaliplatin during HIPEC (460mg/m²) is accepted, the exact procedure of HIPEC can differ between institutions and surgeons. There is no consensus about the usefulness of flushing the HIPEC system with crystalloids at the end of oxaliplatin administration. Flushing is predominantly applied with the idea to minimize both systemic exposure and personnel exposure. On the other hand, HIPEC without flushing might increase effectiveness because intraperitoneal tumour cells might be exposed to oxaliplatin for a longer time period. The option of flushing is based on individual preferences of the surgeon. There is no standardized procedure for flushing after HIPEC. If a surgeon decides to flush after HIPEC the volume and time of flushing differs between patients and between surgeons. There is a lack of knowledge on the effect of flushing on tumour tissue exposure, systemic exposure and wound exudate platinum concentration. Therefore we want to perform a study to investigate the effect of flushing after HIPEC on tissue exposure, systemic exposure and wound exudate platinum concentration. The results of this study will help to further optimise and standardize the HIPEC procedure.

2. OBJECTIVES

Primary objective:

1. To determine the effect of flushing after HIPEC on tissue platinum exposure

Secondary objectives:

2. To explore the effect of flushing after HIPEC on wound exudate platinum concentration
3. To explore the effect of flushing after HIPEC on systemic unbound platinum exposure
4. To explore the relation between the platinum concentration in instillate on total tissue platinum exposure
5. To explore the relation between the platinum concentration in instillate on systemic unbound platinum exposure
6. To explore the effect of the degree of cytoreduction on systemic unbound platinum exposure

3. STUDY DESIGN

Patients

Eligible patients for study entry include patients with a diagnosis of peritoneal carcinomatosis as a result of intra-abdominal cancers who are already planned for HIPEC treatment with oxaliplatin as part of routine clinical care. To determine the effect of flushing after HIPEC on tissue exposure (primary objective) a group of 10 patients are needed who undergo HIPEC with flushing afterwards. To explore the differences of flushing vs. non-flushing (secondary objectives) 10 more patients are needed who undergo HIPEC without flushing afterwards. Cytoreductive surgery and HIPEC will be performed according to the standard local procedure.

Flushing

Flushing after HIPEC will be performed in the first 10 patients. Flushing will be performed immediately after evacuation of the instillate. In this study the abdominal cavity will be flushed during 5 minutes with 2L/m² of sodium chloride 0.9%.

PCI score

To explore the effect of the degree of cytoreduction on systemic exposure of unbound platinum it is necessary to objectively classify the extensiveness of the peritoneal cancer and thereby the intensity of the surgical intervention. As part of routine work the peritoneal cancer index (PCI) is assessed prior to cytoreduction.

CC-score

To completeness of cytoreduction score (CC-Score), as described by Jacquet et al (29), is used to score the completeness of the surgery. A CC-0 score indicates that no macroscopic peritoneal tumour remains after cytoreduction, a CC-1 score indicates that persisting tumour nodules are < 2.5 mm, a CC-2 score indicates residual tumour nodules between 2.5 mm and 2.5 cm and a CC-3 score indicates tumour nodules > 2.5 cm or a confluence of unresected tumour. All patients who do not achieve a CC-0 score will be excluded.

Peritoneal tissue samples

Two 5-cm diameter non-tumour peritoneal tissue samples will be taken from all patients that underwent HIPEC with flushing afterwards. The first sample will be taken immediately after the instillate solution is evacuated from the abdominal cavity. The second sample will be taken immediately after flushing. In the group of patients receiving HIPEC without flushing one 5-cm diameter non-tumour peritoneal tissue sample will be taken immediately after the instillate solution is evacuated from the abdominal cavity. Immediately after resection, all tissue samples will be touched to filter paper in order to remove excess surface fluid. The processing of the tissue will be performed according to the method described by Elias et al. The concentration in non-tumour peritoneal bathed tissue is a good reflection of tumour bathed tissue (9).

Peritoneal fluid samples

To determine the decrease in concentration of unbound platinum concentrations in the heated peritoneal instillate three different 5ml fluid samples will be collected at the following time points: 5 minutes after the start of the HIPEC procedure, 15 minutes after the start of the procedure and at the end of the HIPEC procedure. Based on the measurements in these samples it is possible to follow the decrease of unbound platinum concentrations in the heated peritoneal instillate. An additional 5ml fluid sample will be taken from the sodium chloride 0.9% flush solution at the end of flushing, to determine unbound platinum concentration in the flushing fluid.

Blood samples

A total of thirteen 10ml heparinised blood samples will be collected from each patient. Each sample will be centrifuged within 10 minutes after collection for 5 minutes (1,000 g, 4°C) to separate plasma. Unbound platinum will be obtained by centrifuging the plasma fraction through a 30 kDa cut-off ultrafiltrate filter for 15 minutes (1,000 g, 20°C). Unbound platinum from plasma is performed as soon as possible after blood collection, to prevent a decrease of Pt levels due to progressive *ex vivo* binding of Pt to plasma proteins and erythrocytes. The unbound platinum will be stored at -20°C until analysis. The first three blood samples will be taken at 10, 20 and 30 minutes after the start of HIPEC. The other ten samples will be taken at ¼, ½, 1, 2, 4, 12, 24, 36, 48 and 72 hours after completion of the HIPEC procedure.

Total unbound platinum concentrations will be measured. The individual AUCs are calculated with a trapezoidal approach.

Wound exudate samples

After the HIPEC procedure in the majority of patients one or more drains will be placed. The wound exudate is collected in drainage bottles. Each bottle is changed after 24 hours. This is the moment that personnel can be exposed to contaminated wound exudate. Each drain will produce around 100ml on the first day. The total volume of wound exudate per drain will be measured. A 5 ml sample of wound exudate will be collected from every drain bottle to determine total and unbound platinum concentration. Platinum concentrations will be measured with AAS in The Cancer biology laboratory, Institut Universitaire du Cancer de Toulouse (IUCT) Oncopole.

Duration and setting of the study

The study takes place at Radboud University Medical Centre in Nijmegen, the Netherlands. The study is expected to start in November 2017 and is expected to be completed within 1 year after study initiation.

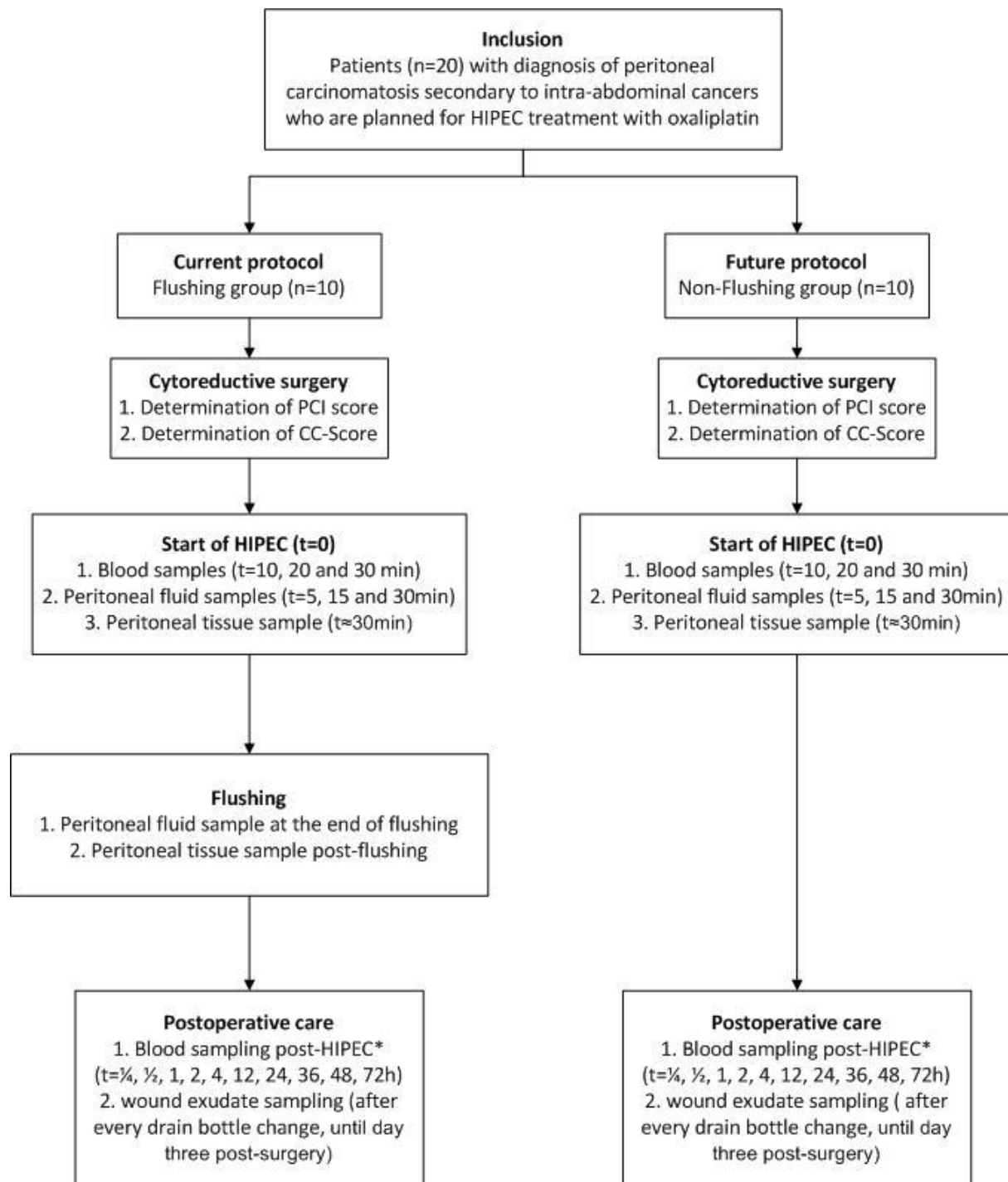


Figure 1. Schematic overview of the study design.

* t₀ is the moment that the instillate is evacuated from the abdominal cavity (the end of HIPEC)

4. STUDY POPULATION

4.1 Population (base)

Eligible patients for study entry include patients with a diagnosis of peritoneal carcinomatosis as a result of intra-abdominal cancers who are already planned for HIPEC treatment with oxaliplatin as part of routine clinical care. In Radboud University Medical Centre an average number of one patient per week is being treated with cytoreduction and HIPEC with oxaliplatin. Therefore, it is expected that the planned number of patients (n=20) can be recruited from this group of patients.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- 1) Subjects must provide written informed consent prior to performance of study-specific procedures or assessments and must be willing to comply with treatment and follow-up.

Note: Informed consent may be obtained prior to start of the specified screening window.

Note: Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes.

- 2) Age ≥ 18 years
- 3) Confirmed diagnosis of preoperatively identified primary or recurrent peritoneal carcinomatosis (PC) of colorectal origin who are planned for HIPEC treatment with oxaliplatin according to routine clinical care

4.3 Exclusion criteria

Patients who do not achieve a cytoreduction score of CC-0 will be excluded from the study.

4.4 Sample size calculation

The primary objective of the study is to determine the effect of flushing after HIPEC on tissue exposure of total platinum content. Therefore the difference in tumour exposure within the same subject before and after flushing will be studied. A difference of $\geq 25\%$ is considered as clinically relevant. For the sample size calculation we used an intra-patient variability in tumour exposure of 20%. A sample size of 10 patients is required to show a difference of $\geq 25\%$ (90% confidence interval) with a power of 90% and a one-side significance level of 0.05.

This study will serve as an exploratory study for all secondary objectives. Therefore no sample size calculation for these objectives has been performed. To make a good comparison possible between flushing and non-flushing we include 10 patients who will undergo HIPEC without flushing.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Cytoreductive surgery combined with HIPEC is performed according to local standard treatment (APPENDIX 1).

5.2 Use of co-intervention

Not applicable.

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable. Oxaliplatin is the standard primary HIPEC treatment.

7. NON-INVESTIGATIONAL PRODUCT

Cytoreductive surgery combined with HIPEC is performed according to local standard treatment (APPENDIX 1). One and a half hour before the intraperitoneal administration of oxaliplatin, the patient is treated with an intravenous infusion of folic acid in a dose of 20mg/m^2 administered over 30 minutes. One hour prior to the beginning of IPCH the patient is treated with 5-FU in a dose of 400mg/m^2 administered in 60 minutes to augment the effects of hyperthermic intraperitoneal oxaliplatin. According to local protocol HIPEC is performed using an open abdominal cavity procedure with the skin pulled upwards (coliseum technique). The abdominal cavity is filled with 5% dextrose. 2500IU of heparin are added to this solution. After 5-FU is administered and the instillate solution has reached a temperature of $41\text{-}42^\circ\text{C}$, oxaliplatin is administered in a dose of 460 mg/m^2 . Oxaliplatin is delivered by the pharmacy in a 5% dextrose solution in the exact dose required for the patient in a concentration of 2mg/ml . Duration of IPCH is 30 minutes.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- The main study endpoint is to show a difference in tissue platinum exposure of $\geq 25\%$ before and after flushing. Tissue platinum exposure is expressed in concentration platinum per milligram tissue (ng/mg).

8.1.2 Secondary study parameters/endpoints

- To explore the difference in total platinum wound exudate concentration between patients with and without flushing after completion of HIPEC
- To explore, quantify and describe the effect of flushing after HIPEC on systemic unbound platinum exposure
- To explore, quantify and describe the effect of platinum concentration in instillate on tissue platinum exposure
- To explore, quantify and describe the effect of the degree of cytoreduction on systemic unbound platinum exposure
- To explore, quantify and describe the effect of platinum concentration in instillate on systemic unbound platinum exposure

8.1.3 Other study parameters (if applicable)

The following parameters are collected at baseline: date of birth, gender, ethnicity, medical history (including gastrointestinal resections if applicable), body height and weight and current medication.

Furthermore patients will be asked about AEs. Laboratory tests for hematology and biochemistry will be performed as part of routine clinical care.

8.2 Randomisation, blinding and treatment allocation

As this is an open label study, blinding procedures are not applicable. A total of 20 patients will be included in the study. The first 10 included patients belong to the *flushing* group and the last 10 included patients belong to the *non-flushing* group.

8.3 Study procedures

After the patient has given written informed consent, each patient will undergo an enrolment medical examination in the 14 days prior to the HIPEC procedure. In table 1 a summary is listed of the parameters that should be collected prior to the HIPEC procedure.

Table 1: summary of study procedures during the study

Procedure	Baseline	Day 1	Day 2	Day 3
<i>Time window</i>	-14d			
Informed consent form	X			
Demographics ^a	X			
Medical history/progress notes	X			
Concomitant medication and herbs	X			
Treatment toxicity/ AEs (CTCAE v4.0)				
Routine laboratory tests ^b	X	X	X	X
Pharmacokinetics ^c		X	X	X
Tissue sampling		X		
Exudate sampling		X	X	X
Electrocardiogram	X	X		

- a. Date of birth, gender, ethnicity, body weight, body height and current smoking status.
- b. Including Karnofsky performance status (see APPENDIX 2).
- c. Oxaliplatin administration at the hospital, blood samples at 10, 20 and 30 minutes after the start of HIPEC and at ¼, ½, 1, 2, 4, 12, 24, 36, 48 and 72 hours after completion of the HIPEC procedure.

The study procedures overview is given in APPENDIX 3. The study procedures overview displays in detail the days and time-points for PK blood sampling, collection of peritoneal fluid samples, resection of peritoneal tissue and collection of wound exudate. Patients have to come to the hospital at screening and the day prior to the day of surgery. After surgery patients stay for approximately one to two days on the intensive care unit. After the study ended the effect of the cytoreduction and HIPEC procedure will be evaluated according to standard treatment care.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

Patients who do not achieve a cytoreduction score of CC-0 will be excluded from the study and replaced by another patient. Patients will be replaced if only <50% of the required pharmacokinetic samples can be collected for any reason. A maximum number of 10 patients will be replaced.

8.6 Follow-up of subjects withdrawn from treatment

Patients will be followed up conform standard routine care. Besides standard clinical care, no additional follow-up for study purpose is required.

8.7 Premature termination of the study

Not applicable. Patients are treated according to routine and consolidated clinical car

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events as consequence of the additional sample collection in this study that are reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs as consequence of the additional sample collection in this study to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Patients who participate in the study will receive standard treatment conform local procedure. All SUSARs will therefore be handled following standard work procedure. The SUSAR will be reported directly to Lareb (the Netherlands Pharmacovigilance Centre) and Lareb will take care of the data input in EudraVigilance.

9.3 Annual safety report

The sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs will be reported till end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Regarding the nature of this study no data safety monitoring board will be appointed.

10. DATA ANALYSIS

10.1 Bioanalysis

Platinum concentrations in blood, instillate, exudate and tissue samples will be analyzed at the Cancer biology laboratory in Toulouse or in the Bioanalytical Laboratory of the Netherlands Cancer Institute in Amsterdam. The Cancer biology laboratory uses validated flameless atomic absorption spectrophotometry to measure platinum concentrations (30). The Bioanalytical Laboratory of the Netherlands Cancer Institute uses a validated method based on quantification of Pt by inductively coupled plasma mass spectrometry (31-33).

10.2 Statistical analysis

10.2.1 Primary study parameter(s)

The main study endpoint is to show a difference in tumour platinum exposure of $\geq 25\%$ before and after flushing. The tissue platinum exposure before and after flushing will be compared by performing a paired sample t-test.

10.2.2 Secondary study parameter(s)

- To explore the difference in platinum wound exudate concentration between patients with and without flushing after completion of HIPEC: mean wound exudate concentrations will be calculated for both groups (flushing vs. non-flushing). An independent t-test will be performed to explore differences.
- To explore, quantify and describe the effect of flushing after HIPEC on systemic exposure of oxaliplatin: The mean AUCs of unbound platinum will be calculated. AUCs of flushing vs. no flushing will be compared by performing an independent t-test
- To explore, quantify and describe the effect of platinum concentration in instillate on tissue platinum exposure: Regression analysis will be performed to model the relationship
- To explore, quantify and describe the effect of the degree of cytoreduction on systemic unbound platinum exposure: Regression analysis will be performed to model the relationship
- To explore, quantify and describe the effect of platinum concentration in instillate on systemic unbound platinum exposure: Regression analysis will be performed to model the relationship

PK parameters for unbound platinum (AUC_{0-72h} , C_{max} and t_{max}) will be calculated by non-compartmental analysis. After finalizing the study the data will additionally be analyzed by Nonlinear mixed effect modeling to estimate the PK parameters for the population and the individual patients.

Based on the individual concentration-time data, the following PK parameters will be determined (non-compartmental analysis).

AUC_{0-72h} : the area under the unbound platinum concentration-time curve calculated (linear trapezoidal method) until the last measurable platinum concentration.

C_{max} : the maximum unbound platinum drug concentration

t_{max} : the time to reach maximum unbound platinum drug concentration.

Individual and mean unbound platinum concentrations will be presented. Overlay presentations will be given to illustrate intersubject variability. Descriptive statistics will be used to calculate the unbound platinum concentration at each sampling time.

10.2.3 Other study parameters

Descriptive statistics will be performed for demographics collected at baseline.

10.2.4 Interim analysis

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Seoul, Tokyo, Venice, Hong Kong, South Africa and Edinburgh), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

11.2 Recruitment and consent

Eligible patients will be asked for participation by their treating physician or a committed research nurse. A patient information folder with extensive information will be handed out to possible subjects. It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The investigator must utilize an IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the persons obtaining consent.

An oral summary of the most important topics (e.g. the burden and the right to withdraw without consequences) will be given before screening, including time for additional questions. If necessary, additional time to (re)consider participation will be provided.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Benefits associated with participating in this study are that patients and their treating physician get insight into the effect of flushing after HIPEC on tumour exposure.

Patients who participate in the study will receive standard treatment conform local protocol. Therefore the risk for participation in this study is regarded negligible. Collection of peritoneal fluid, blood, and wound exudate samples do not put patients at risk or interfere with standard treatment. In the group of patients receiving HIPEC with flushing two 5-cm diameter non-tumour peritoneal tissue samples will be taken prior to and at the end of flushing. In the group of patients receiving HIPEC without flushing one 5-cm diameter non-tumour peritoneal tissue sample will be taken prior to abdominal closure. Compared to the complexity and amount of cytoreduction that is performed during surgery this can be considered as a minor procedure.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Subjects will receive no compensation for participating in the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Blood samples for PK analysis will be identified by study name, patient number, date and time of sampling and sample code. The medical record and other source documents are only accessible by the medical staff of the clinical research centre, the investigator and monitor. CRFs do not contain identifiable information and will be coded with randomization numbers only. Information and study files that are necessary for the evaluation of the research are stored anonymously and the identification key will not be accessible by unauthorized parties.

12.2 Monitoring and Quality Assurance

The monitor will be a staff member at the Pharmacy at the Radboud University Nijmegen Medical Centre. The monitor will work independently and has no involvement in the set up of the study, the conduct of the study and interpretation of the results.

Monitoring consists of:

- check essential documents at the site
- check eligibility of subjects prior to study start
- monitoring for completeness and correctness of the source documents
- monitoring of the data in the workbook, and transfer of data from source documents to the CRF
- write monitoring reports

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions as consequence of the additional sample collection, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The study will be registered to a publicly accessible registry and results database (ClinicalTrials.gov). The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 7 days prior to submission of the publication or presentation to all co-investigators.

12.7 Sample destruction after study completion

Any samples left over after analysis will be destroyed when the study is completed. Samples will be discarded in compliance with local biologic waste disposal requirements.

13. STRUCTURED RISK ANALYSIS

Half of the patients who participate in the study will receive standard treatment conform current practice in Radboudumc, HIPEC with flushing afterwards. The other half of the patients will receive standard treatment conform future protocol that will be implemented in the beginning of 2018, HIPEC without flushing afterwards. Because both procedures are currently used in the Netherlands, the additional risk for participation in this study is regarded negligible.

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15. Appendix

APPENDIX 1: Radboudumc protocol primary HIPEC with oxaliplatin and 5-FU

Checklist kuurnaam/nummer: Primaire HIPEC met oxaliplatin en 5FU

Indicatiegebied: Peritoneale metastasen van colorectale carcinomen, appendixcarcinomen, recidief na primaire HIPEC

Contra-indicaties:

Beenmergdepressie bij begin van de eerste kuur, gedefinieerd als neutrofiële granulocyten $< 2 \times 10^9/l$ en/of trombocyten $< 100 \times 10^9/l$. Perifere sensitieve neuropathie met functieverlies bij aanvang van de eerste kuur. Ernstige nierinsufficiëntie (creatinineklaring < 30 ml/min). Ernstige leverfunctiestoornissen. Bewezen DPD-deficientie.

Kuur medicatie:

Geneesmiddel	Dagdosis	Dag	cyclusduur	Toedieningswijze
Oxaliplatin	460 mg/m ²	1	eenmalig	i.p, opgelost in minimaal volume glucose 5% (max. concentratie 2mg/ml)
Folinezuur	20 mg/m ²	1	Eenmalig	i.v. opgelost in 100 ml NaCl 0,9%
5FU	400 mg/m ²	1	Eenmalig	i.v. opgelost in 50 ml NaCl 0,9% in 4 minuten

Anti-emetica:

Schema 2	Dag 1	Dag 2-3	Dag 4
	Dexamethason 1 dd 8 mg	Dexamethason 1 dd 8mg	geen
	Ondansetron 1 dd 8 mg		

Standaard laboratorium onderzoek:

Vooraf aan start behandeling	Smartset A
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Toxiciteit:

5FU: hand-voet syndroom, diarree, reversibele hyperbilirubinemie (meestal indirecte fractie), en minder frequent beenmergsuppressie, alopecia, misselijkheid, braken.

Oxaliplatin: (meestal) reversibele sensibele neuropathie, beenmergsuppressie, misselijkheid, braken, diarree, stomatitis, zelden allergische reacties.

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Bijzonderheden:

Voorafgaand aan de CRS-HIPEC procedure dienen alle patiënten gezien te zijn door de medisch oncoloog. De medisch oncoloog is verantwoordelijk voor het voorschrijven van de chemotherapie.

Referenties:

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Toedieningsschema tweede lijns HIPEC

Starttijd lijn 1		Medicatie	Dosering protocol	Route	Oplosmiddel	Inlooptijd
00:00		Dexamethason Samen met ondansetron	8 mg + 8mg	i.v.	50 ml NaCl 0.9%	00:15
00:30		folinezuur	20mg/m2	i.v.	100 ml NaCl 0.9%	00:30
01:00		5-fluorouracil	400mg/m2	i.v.	50 ml NaCl 0.9%	01:00
	Starttijd lijn 2 (IP)					
	02:00	Oxaliplatin	460mg/m2	i.p.	Glucose 5% eindconcentratie 2 mg/ml – minimaal volume	01:30

*PAS OP voor i.p. lijn voor en naspoelen met glucose 5% - oxaliplatin is onverenigbaar met NaCl 0,9%

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Eerste lijns HIPEC : Oxaliplatin

De spoeling met Oxaliplatin wordt gecombineerd met peroperatieve systemische chemotherapie met Leucovorin (Folinezuur) en 5-FU (cytostaticum). De Leucovorin wordt 1 ½ uur voor spoeling intraveneus toegediend in een dosis van 20 mg/m² in 30 minuten. De 5-FU wordt 1 uur voor het begin van de spoeling i.v. toegediend in een dosis van 400 mg/m² 250 ml NaCl 0,9% in 1 uur. (Leucovorin/ 5-FU: actie anesthesie).

- Het abdomen wordt vanuit de machine gevuld met 5% glucose oplossing. Hieraan toevoegen 2500 i.e. heparine. Oxaliplatin wordt door de apotheek afgeleverd in een infuuszak van 300-500 ml fysiologisch zout. Deze infuuszak wordt aangesloten op het reservoir van de spoelset. Toevoeging van de intraperitoneale Oxaliplatin kan starten wanneer de i.v. chemotherapie volledig is toegediend en de perfusievloeistof een temperatuur van 41-42° C heeft bereikt. De totale dosis van 460 mg/m² wordt in één gift toegevoegd. De totale duur van de spoeling is 30 minuten (i.t.t. mitomycine (=90 minuten))

Tweede lijns HIPEC : Mitomycine C

Tweede lijns HIPEC met mitomycine C wordt gegeven als patiënt na CR en HIPEC met Oxaliplatin voor een recidief behandeld wordt met CR en HIPEC. Het HIPEC systeem wordt gevuld met dialyse vloeistof (Physioneal) , 2500 i.e. heparine en 10 ml KCl 7.5% en opgewarmd tot 43° C. Na aansluiten via de drains op de buikholte , deze opwarmen tot 42° C.

De Mitomycine C wordt toegevoegd aan de dialyse vloeistof als de juiste temperaturen zijn bereikt. Er wordt 90 minuten geperfundeed met chemotherapie.

- Mitomycine C dosering : 35 mg/ m² lichaams oppervlak. Te verdelen over 3 doseringen. De maximale dosering gaat uit van een lichaamsoppervlak van 2 m². Dus bij een patiënt met een groter lichaamsoppervlak dan 2 m² wordt maximaal 70 mg in 3 dosis gegeven.
- De totale dosis wordt verdeeld over 3 injectiespuiten die door de apotheek worden klaargemaakt:
 - 1^e gift : 50% van de totale dosis Mitomycine C wordt gegeven als de temperatuur in de buikholte 42° C is.
 - 2^e gift : 25% van de totale dosis Mitomycine C wordt gegeven 30 minuten na de eerste gift.
 - 3^e gift : 25% van de totale dosis Mitomycine C wordt gegeven 60 minuten na de eerste gift.

Bij huidcontact met een van bovengenoemde cytostatica : spoelen met (veel) kraanwater.

Per oktober 2014 is 1^e lijns medicatie Oxaliplatin geworden i.p.v. Mitomycine C

Bron : Protocol HIPEC (OK)

5 november 2015

HIPEC

Werkinstructie, OK Heelkunde (HEELK)

Indicatie ingreep

Patiënt met carcinosis peritonei op basis van colorectaal carcinoom of pseudomyxoma peritonei of mesothelioom. Er vindt preoperatief een selectie plaats en patiënt stemt in met Hipec ingreep. Patiënt krijgt bij sommige protocollen oxaliplatin of cisplatinum+doxorubicine of Mitomycine C.

Controleer aan het begin van de dag. Alle chemotherapie moet met de patiënt meekomen vanaf de afdeling. Chemo wordt kant en klaar geleverd door de apotheek in een grijze chemokist. Deze kist hoort met de patient mee te komen van de verpleegafdeling naar de operatiekamer. Als deze niet op het bed aanwezig bij aankomst van de patient op de OK, checken bij de verpleegafdeling (tel 13438), anders navragen bij de apotheek. Controleer de houdbaarheid van alle cytostatica. Tijdstip houdbaarheid chemo doorgeven bij time out en opschrijven op het bord.

Ligging patiënt

Op de operatietafel komt op een saharalaken te liggen. Patiënt heeft steunkousen aan. Patient wordt nadat de epiduraal catheter, een lieslijn en een centraal veneuze lijn heeft gekregen in de beensteunen gelegd. De diathermieplaat wordt dwars op het rechter bovenbeen geplaatst zodat de klip net niet onder de kous valt en naar beneden kan wegklappen. Op de diathermie plaat wordt de lieslijn bevestigd.

Zie voor algemene informatie: [Positionering van de patiënt op de operatietafel](#)

Desinfecteren

Patiënt desinfecteren vanaf tepellijn tot os pubis. Perineum poetsen met chloorhexidine. Bij vrouw ook een vaginaal toilet met betadine jodium.

Afdekken

Alle afdekmaterialen gebruiken van de firma Medline. Zijdoekje onder de stuit plaatsen. Twee zijdoekjes aanbrengen. Per been wordt een groot laken over het been gedrapeerd. Groot laken vanaf tepels naar boven plaatsen. opvangzakje plaatsen onder de anus. Ioban steridrape over buik plaatsen. Deze beide zijn bedoeld om eventueel druppels tijdens spoelen op de grond te voorkomen.

Extra benodigdheden

Bij toepassing van oxaliplatin de dag vantevoren 6 stuks Glucose 5% 1000ml infusievloeistof klaarleggen in de warmtekast. Bij de toepassing van Mitomycine C wordt de dag van tevoren Physioneal 35 van Baxter klaargelegd.

Zorg ervoor dat er voldoende NaCl spoelvloeistof klaarligt.

Hipec aandachtspunten

Bij een Hipec zorg je ervoor dat alle spullen die nodig zijn tijdens het spoelen al op de ok liggen tijdens de debulking. De hipec-brillen, schoenhoezen, maskers, jassen, celstofmatjes en groene matten op de ok plaatsen.

Oxaliplatinprotocol: Er wordt gestart met de debulking zonder gebruik te maken van chemostatica. Tijdens deze fase geen extra beschermende maatregelen.

In overleg met de operateur wordt er gestart Folinaat (Leucovorin 20 mg/m²) in 100 ml NACL 0,9%. Dit loopt intraveneus in 30 minuten in. Dit is foliumzuur en is dus nog geen chemo, (dit heet ook Rescuvolin 5 ml = 50 mg) ligt in koelkast in anaesthesieruimte. In overleg met de operateur wordt er gestart met intraveneuze chemo. Fluouracil (5FU 400 mg/m²) in 250 ml NACL 0,9%) wordt aangesloten en zal in 60 minuten inlopen. Daarna het infuus doorspoelen met NACL.

Hierna kan er gestart worden met de peritoneale perfusie.

Het abdomen wordt gevuld met Glucose oplossing. Toediening van de Oxaliplatin kan starten wanneer de i.v. chemotherapie volledig is toegediend en de perfusievloeistof een temperatuur heeft bereikt van 42-43°C. Het spoelen met Oxaliplatin duurt 30 minuten.

Vanaf het inspuiten of het lopen van het perfusaat met chemo worden de preventieve absorberende onderleggers geplaatst. Het opererend team trekt reinforced jassen en dubbele Biogel handschoenen aan. De omloop trekt de blauwe omloopjas, bril en eventueel de schoenhoezen aan.

De instrumenterende gaat vanaf het inlopen van de Fluouracil of na het begin van het spoelen van de buik met chemo de gazen als besmet beschouwen en verzamelt alle gazen in een grote kom.

Mitomycine C protocol: toediening in perfusievloeistof in drie giften toegevoegd aan het perfusaat, perfusie gedurende 90 minuten.

Cisplatinum+doxorubicine protocol: volgens instructie van de operateur

Perfusionist werkt bij de Hipec met het Medtronic gemodificeerde heater/cooler. Je gebruikt dan dus ook de Medtronic hipec kit.

De perfusionist heeft ongeveer 45 minuten nodig voor aanvang van het peritoneaal spoelen zodat het apparaat opgebouwd kan worden en de vloeistof opgewarmd kan worden.

Risico en bescherming:

Blootstelling aan cytostatica wordt voorkomen door het nemen van de juiste veiligheidsmaatregelen. Het belangrijkste gevaar is besmetting van het cytostaticum door huid of oogcontact (direct of door beschadiging/perforatie van handschoenen, kleding of oogbescherming of door spatten of morsen) of accidenteel inslikken (bijvoorbeeld via besmette handen)

Beschermende maatregelen:

Saharamat op de ok tafel
Voor aanvang cytostatica bordjes op ok deur.
Beschermende bril (3M)
Mondmasker, elk mondmasker is afdoende, de cytostatica kent geen dampfase en zal zich dus niet in de lucht bevinden.
Impermeabele (reinforced) ok jas
Eventueel schoenhoezen
dubbele latexhoudende Biogel handschoenen tijdens en na het spoelen. Bij spoelen over de dubbele handschoenen de lange ellebooghandschoenen dragen om lekkage via de manchetten te voorkomen. Is de patiënt overgevoelig voor latex dan biogel underglove (blauwe handschoen) en daaroverheen biogel skinsense.
Waterafstotend afdek materiaal
Plastic kap boven buikholte om spatten te voorkomen
Preventieve absorberende onderleggers op de grond
Afvalcontainers voor afval die geproduceerd wordt na het spoelen met cytostatica
Na de ok de spatzone poetsen met disposable poetsdoeken, deze na gebruik weggooien in de risicoton.
Instrumentensets gaan in instrumentenkar, deze worden door operatie-assistenten afgevoerd naar de vuile dienst.
Veegproeven incidenteel (ongeveer 1x per jaar) en als hier aanleiding voor is

Handelen bij calamiteiten

Bij huidcontact: spoelen met veel (kraan) water
Bij oogbesmetting: oog spoelen met oogdouche
Zie acute koffer.

Instrumentarium

Als de instrumenterende links staat.

Van linksonder naar rechtsonder:

- Mes 20, twee gilles pincetten, mayo schaar, metzembaum schaar kort en lang, debakey kort en lang, 2 lang chirurgische pincetten, 8 crile klemmen en 2 kochers.

Rechtsmidden:

- Gazen

Linksmidden:

- Naaldvoerders lang en kort

Van linksboven naar rechtsboven:

- Monihan fijn en groot, heiss klem kort en lang, mitteldorp haken en scherpe haken.

Verloop ingreep

Cytoreductieve chirurgie. Hierbij is het doel om zoveel mogelijk te verwijderen van macroscopische tumordeposities van het visceraal en parietale peritoneum, zonodig met multiviscerale resectie. Dit is per patiënt erg verschillend.

Tijdens of vooraf aan de debulking worden voorbereidingen gemaakt voor het spoelen. nl:
Ok assistent bevestigt op twee plaatsen 4 thermometers aan 4 Abdovac FG 18 met vicryl 2.

De thermometers steken ietsje uit tov de drains.

Op de outflowdrain wordt de dreesman zuiger geplaatst nadat de gaten van de drain zijn afgeknipt. De outflowdrain en de temperatuurmeters worden na het spoelen verwijderd uit de buik.

Chirurg hangt de buikwand op met doekklemmen en tie-wraps aan de Booklerspreider. Hierdoor wordt de buik omhooggespannen en kun je een diepere holte creëren. De temperatuursondes worden aangesloten op temperatuurmeter van het perfusieapparaat. Deze temperatuurmeter inpakken in een steriel camerahoes.

Via de slangenset worden de invoerdrains aangesloten op het perfusieapparaat. Bij de slangenset de invoerregelaars opschuiven naar de plaats waar de connectie wordt gemaakt. Er wordt gekeken of de drains op de goede plaats liggen. Aan de hand van de temperatuurmeting wordt gekeken of er een goede invoer van vloeistof is in de buik. De uitvoerslang wordt ook bevestigd aan het perfusieapparaat. Er wordt een hoos aangebracht over de spreider, dit om spatten te voorkomen.

Bij start van de Oxiplatin of Mitomycine C verdwijnen er zoveel mogelijk mensen uit de ok. De pa –preparaten worden ingestuurd. De anaesthesist of anaesthesie-assistent blijft op de ok. De perfusionist bedient het apparaat. De operateur komt roeren in de buik van de patiënt. Het spoelen duurt 30 minuten.

Beschermende maatregelen: spatbril, jas, sloffen, masker en dubbele biogel handschoenen met daaroverheen ellebooghandschoenen. Tijdens het spoelen wordt het gebruikte instrumentarium in een kom met H2O gelegd.

Na het spoelen volgt eventueel de reconstructie door een darmnaad of een anus preaternalis aan te leggen. Daarna wordt de fascie gesloten, de huid wordt gesloten met huidnietjes.

De drainflessen worden zorgvuldig bevestigd aan de drainpotten. Deze drainopeningen netjes afplakken met hansapor en grip lok.

Bij de hipec worden aan het eind van ingreep alle instrumenten in een instrumentenkar geplaatst. Deze kar plaatsen in de vuile ruimte.

Nadat de patiënt is overgeschoven op het patiëntenbed een nieuwe unometer aansluiten. Doe dit voorzichtig om contaminatie te voorkomen.

De risicotonnen plaatsen met sticker in de vuile dienst.

Wondverzorging

Wonden afplakken en stomazakje plakken.

Bijzonderheden

Perfusionisten: Andre gelsing: *81-2115
Laura Scholte: *81-2114
Paul Wessel: *81-2111

Apotheek: 16305, apothekersassistente: *81 3187

Telefoon restaurant: 06-55270500.

Asito om de OK te laten poetsen: 06-27211371 of er wacht iemand totdat de OK klaar is.

APPENDIX 2: Karnofsky Performance Status Scale Definitions Rating Criteria

WHO/ECOG Performance Status		Karnofsky Performance status scale	
0	Able to carry out all normal activity without restriction	100	Normal no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self; unable to carry on normal activity or to do active work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his personal needs.
		50	Requires considerable assistance and frequent medical care.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospital admission is indicated although death not imminent.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair	20	Very sick; hospital admission necessary; active supportive treatment necessary.
		10	Moribund; fatal processes progressing rapidly.
5	Dead	0	Dead

APPENDIX 3: Study procedures overview

Procedure	Flushing group				
	Screening	Time relative to the day of surgery			
	Day -14 until day 0	Day 0	Day 1	Day 2	Day 3
Written informed consent	X				
Inclusion/exclusion criteria	X				
Anamnesis/ medical history	X				
Demography	X				
Concomitant Medications	X				
Laboratory clinical chemistry	X				
Cytoreduction and HIPEC with flushing afterwards ¹		X			
Blood PK sampling ²		X	X	X	X
Peritoneal PK sampling ³		X			
Tissue collection ⁴		X			
Wound exudates sampling ⁵		X	X	X	X

¹ flushing is performed with 2L/m² of sodium chloride 0.9% during 5 minutes

² blood samples (timepoints relative to the start of HIPEC): 10min, 20min, 30min, 45min, 1h, 1½ h, 2h, 4h, 12h, 24h, 36h, 48h, 72h.

³ peritoneal samples (timepoints relative to the start of HIPEC): oxaliplatin solution: 5min, 15min, 30min; flushing solution: 45min.

⁴ tissue samples of peritoneum: pre- and post-flushing

⁵ wound exudate samples will be taken each time a drain bottle is changes. Sampling continues until the drain is removed or until day 3 post-HIPEC has been reached.

Procedure	Non-flushing group				
	Screening	Time relative to the day of surgery			
	Day -14 until day 0	Day 0	Day 1	Day 2	Day 3
Written informed consent	X				
Inclusion/exclusion criteria	X				
Anamnesis/ medical history	X				
Demography	X				
Concomitant Medications	X				
Laboratory clinical chemistry	X				
Cytoreduction and HIPEC without flushing afterwards ¹		X			
Blood PK sampling ²		X	X	X	X
Peritoneal PK sampling ³		X			
Tissue collection ⁴		X			
Wound exudates sampling ⁵		X	X	X	X

¹ no additional flushing is performed

² blood samples (timepoints relative to the start of HIPEC): 10min, 20min, 30min, 45min, 1h, 1½ h, 2h, 4h, 12h, 24h, 36h, 48h, 72h.

³ peritoneal samples (timepoints relative to the start of HIPEC): oxaliplatin solution: 5min, 15min, 30min

⁴ tissue sample of peritoneum after evacuation of oxaliplatin-solution

⁵ wound exudate samples will be taken each time a drain bottle is changed. Sampling continues until the drain is removed or until day 3 post-HIPEC has been reached.