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ClinicalTrials.gov ID: NCT02567253

Study Identification

Unique Protocol ID:	AGO/2015/002
Brief Title:	Intraoperative Intraperitoneal Chemoperfusion to Treat Peritoneal Minimal Residual Disease in Stage III Ovarian Cancer (OvIP1)
Official Title:	Intraoperative Intraperitoneal Chemoperfusion to Treat Peritoneal Minimal Residual Disease in Stage III Ovarian Cancer: A Randomized Phase II Trial
Secondary IDs:	

Study Status

Record Verification:	November 2023
Overall Status:	Completed
Study Start:	March 2016 [Actual]
Primary Completion:	December 31, 2020 [Actual]
Study Completion:	August 25, 2021 [Actual]

Sponsor/Collaborators

Sponsor:	University Hospital, Ghent
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
Unapproved/Uncleared Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 21/12/2015 Board Name: Ethics Committee Board Affiliation: Ghent University Hospital Phone: +32 9 332 49 62 Email: Ethisch.Comite@ugent.be Address: De Pintepark II - 2de verdieping De Pintelaan 185

	9000 Ghent Belgium
Data Monitoring:	Yes
FDA Regulated Intervention:	Yes
Section 801 Clinical Trial:	Yes

Study Description

Brief Summary:	The OvIP1 study is designed to examine how drug dose and perfusion temperature affect the pharmacokinetics and pharmacodynamics of cisplatin used as (hyperthermic) intraperitoneal chemoperfusion, as an adjunct to surgery, in women with stage III epithelial ovarian cancer.
Detailed Description:	Stage III ovarian cancer (OC) remains an important cause of cancer related mortality in women. After successful initial treatment, most patients eventually develop recurrent peritoneal disease which can only arise from peritoneal minimal residual disease (pMRD) left after primary cytoreductive surgery (CRS). Intensification of locoregional therapy through intraoperative intraperitoneal chemoperfusion (IPEC) immediately following CRS may prevent or delay peritoneal recurrence. Although IPEC, usually under hyperthermic conditions, is increasingly used in OC, its efficacy and the potential benefit of hyperthermia are at present unknown.The primary aim of this study is to assess the pharmacokinetic and pharmacodynamic properties of IP cisplatin administered under normothermic or hyperthermic conditions, and at different dosing schedules. Additional endpoints include surgery related morbidity and mortality, quality of life, overall survival, disease free survival, peritoneal recurrence free survival, peritoneal cytology, and exploration of potential biomarkers.

Conditions

Conditions:	Ovarian Cancer Primary Peritoneal Cancer
Keywords:	Cytoreductive surgery (H)ipec Ovarian cancer Cisplatin Peritoneal carcinomatosis Pharmacokinetics Pharmacodynamics

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Interventional Study Model:	Parallel Assignment
Number of Arms:	4
Masking:	Single (Participant)
Allocation:	Randomized
Enrollment:	56 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: low dose, normothermic CRS + normothermic (37°C) intraoperative intraperitoneal chemoperfusion, with 75mg/m² Cisplatin during 90min + adjuvant chemotherapy	Procedure/Surgery: Cytoreductive surgery Complete or nearly complete (CC-0 or CC-1) macroscopic cytoreduction at the time of surgery of peritoneal carcinomatosis from ovarian cancer Drug: IPEC with Cisplatin (75mg/m²) Intraperitoneal normotherm (37°C) administration of Cisplatin (75mg/m²) , during 90min
Experimental: high dose, normothermic CRS + normothermic (37°C) intraoperative intraperitoneal chemoperfusion, with 100mg/m² Cisplatin during 90min + adjuvant chemotherapy	Procedure/Surgery: Cytoreductive surgery Complete or nearly complete (CC-0 or CC-1) macroscopic cytoreduction at the time of surgery of peritoneal carcinomatosis from ovarian cancer Drug: IPEC with Cisplatin (100mg/m²) Intraperitoneal normotherm (37°C) administration of Cisplatin (100mg/m²), during 90min
Experimental: low dose, hyperthermic CRS + hyperthermic (41°C) intraoperative intraperitoneal chemoperfusion, with 75mg/m² Cisplatin during 90min + adjuvant chemotherapy	Procedure/Surgery: Cytoreductive surgery Complete or nearly complete (CC-0 or CC-1) macroscopic cytoreduction at the time of surgery of peritoneal carcinomatosis from ovarian cancer Drug: Hypertherm IntraPEritoneal Chemotherapy with Cisplatin (75mg/m²) Intraperitoneal hypertherm (41°C) administration of Cisplatin (75mg/m²), during 90min
Experimental: high dose, hyperthermic CRS + hyperthermic (41°C) intraoperative intraperitoneal chemoperfusion, with 100mg/m² Cisplatin during 90min + adjuvant chemotherapy	Procedure/Surgery: Cytoreductive surgery Complete or nearly complete (CC-0 or CC-1) macroscopic cytoreduction at the time of surgery of peritoneal carcinomatosis from ovarian cancer Drug: HIPEC with Cisplatin (100mg/m²) Intraperitoneal hypertherm (41°C) administration of Cisplatin (100mg/m²), during 90min

Outcome Measures

Primary Outcome Measure:

1. Tissue penetration distance of cisplatin in peritoneal tumor tissue nodules using laser-ablation inductively couples plasma mass spectrometry
   This will be analyzed via laser ablation-inductively coupled plasma- mass spectrometry (LA-ICP-MS)

   [Time Frame: 1 tumor nodule will be immediately fixed in liquid nitrogen after cytoreductive surgery and chemoperfusion. Frozen sections will be ablated through study completion]

Secondary Outcome Measure:

2. Surgical morbidity and mortality will be measured using Dindo-Clavien classification
   This will be estimated with the Dindo-Clavien classification

   [Time Frame: Within 30 days after surgery and intraoperative intraperitoneal chemoperfusion]

3. Cancer-specific Quality of Life-C30
   This will be investigated using the cancer-specific (C30) European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires

   [Time Frame: 3 weeks before operation, 6 weeks after and 3, 6, 12, 18 and 24 months after surgery and chemoperfusion]

4. Disease-specific Quality of Life-OV28
   This will be investigated using the disease-specific (OV28) European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaires

[Time Frame: 3 weeks before operation, 6 weeks after and 3, 6, 12, 18 and 24 months after surgery and chemoperfusion]

5. Maximum perfusate concentration (Cmax) of cisplatin
   Cisplatin (free + bounded) will be measured in perfusate, using high performance liquid chromatography coupled to an inductively coupled plasma- mass spectrometry (HPLC-ICP-MS)

   [Time Frame: T=0min (before chemoperfusion), T=15min, T=30min, T=90min (during chemoperfusion); T=2h, T=3h, T=7.5h, T=24h (after start chemoperfusion)]

6. Maximum plasma concentration (Cmax) and Area Under The Curve (AUC) of cisplatin
   Cisplatin (free + bounded) will be measured in plasma, using high performance liquid chromatography coupled to an inductively coupled plasma- mass spectrometry (HPLC-ICP-MS)

   [Time Frame: T=0min (before chemoperfusion); T=15min, T=30min, T=90min (during chemoperfusion); T=2h, T=3h, T=7.5h, T=24h (after start chemoperfusion)]

7. Pharmacodynamics (PD) of cisplatin will be analyzed by visualizing the amount of DNA double-strand breaks (dsb) via the specific DNA-adduct immunohistochemical Liedert staining
   PD of cisplatin will be studied via Pt-DNA adduct formation, using the Liedert staining which is specific for Pt-[Guanine, Guanine] adducts (Pt-[GG]) using Mab R-C18. The amount of double-strand breaks (dsb) will be analyzed then via fluorescence microscopy

   [Time Frame: 1 tumor nodule will be immediately fixed in 4% paraformaldehyde and immunohistochemical stainings will be done through study completion]

8. Overall survival
   Calculated from date of surgery until death

   [Time Frame: 24 months after finishing the adjuvant chemotherapy]

9. Disease free survival
   Time interval between date of surgery and disease progression or death

   [Time Frame: 24 months after finishing the adjuvant chemotherapy]

10. Peritoneal recurrence free survival
    Time interval between date of surgery and peritoneal recurrence or death

    [Time Frame: 24 months after finishing the adjuvant chemotherapy]

11. Expression analysis of selected biomarkers = Excision repair cross-complementation group 1 (ERCC1), Methylguanine methyltransferase enzyme (MGMT), Breast cancer gene 1 (BRCA1), Copper transporter 1 (CTR1) using quantitative PCR
    Gene expression of potential predictive biomarkers using qPCR

    [Time Frame: 1 tumor nodule will be immediately fixed in liquid nitrogen. Histological coupes will be made through study completion]

12. Stromal composition and density of tumor tissues via analyzing collagen density, fibroblast Proliferation and DNA-intrastrand adduct formation of Pt-[GG]
    Analyzing collagen density using the sirius red staining, analyzing fibroblast proliferation using alfa smooth-muscle action (α-SMA) stainings and DNA intrastrand adduct formation of Pt-[GG] with the Liedert staining using Mab R-C18

    [Time Frame: 1 tumor nodule will be immediately fixed in 4% paraformaldehyde. Histological coupes will be made through study completion]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Sex:	Female
Gender Based:	

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Tumor type:

  * Biopsy proven serous epithelial ovarian carcinoma or peritoneal carcinoma
- Primary or recurrent disease
- Extent of disease:
  - Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis (FIGO stage III, Appendix (47))
  - Stage IV with unilateral pleural fluid allowed
  - Complete or nearly complete macroscopic cytoreduction at the time of surgery (CC-0 or CC-1) deemed possible based on imaging, laparoscopy, or both
- Second-line patients; platinum sensitive
- Age over 18 years
- No major cardiac or respiratory disease
- Adequate performance status (Karnofsky index > 70%)
- Adequate mental faculty, allowing to understand the proposed treatment protocol and provide informed consent
- Expected life expectancy more than 6 months
- Laboratory data:
  - Serum creatinine ≤ 1.5 mg/dl or a calculated Glomerular Filtration Rate (GFR) (CKD-EPI) ≥ 60 mL/min/1.73 m2
  - Serum total bilirubin ≤ 1.5 mg/dl, except for known Gilbert's disease
  - Platelet count > 100.000/µl
  - Hemoglobin > 9g/dl
  - Neutrophil granulocytes > 1.500/ml
  - International Normalized Ratio (INR) ≤ 2
- Absence of alcohol and/or drug abuse
- No other concurrent malignant disease
- No inclusion in other clinical trials interfering with the study protocol
- No concurrent chronic systemic immune or hormone therapy, except neoadjuvant chemotherapy
- Absence of any severe organ insufficiency
- No pregnancy or breast feeding
- Written informed consent

Exclusion Criteria:

- Severe or uncontrolled cardiac insufficiency, including recent (< 6 months) occurrence of myocardial infarction, the presence of congestive cardiac insufficiency, of symptomatic angor in spite of optimal medical care, of cardiac arrhythmia requiring medical treatment presenting insufficient rhythm control, or uncontrolled arterial hypertension
- Pregnancy or breast feeding
- Platinum resistant or refractory disease
- Active bacterial, viral or fungal infection
- Active gastro-duodenal ulcer
- Parenchymal liver disease (any stage cirrhosis)
- Uncontrolled diabetes mellitus
- Severe obstructive or restrictive respiratory insufficiency
- Psychiatric pathology capable of affecting comprehension and judgment faculty
- Tumor in the presence of obstruction
- Evidence of extra-abdominal disease (with the exception of unilateral malignant pleural effusion) or extensive liver metastasis

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IPDSharing

Plan to Share IPD:

References

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Links:

Available IPD/Information: