Predictive factors and pharmacokinetics of intraperitonal chemotherapy

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Primary:• In this project, we propose to study the use of this aspiration fluid from the intraperitoneal cavity as a biomarker for the efficacy of chemotherapy intervention.The research questions for this study are:• Monitor the effect of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational non invasive

Summary

ID

NL-OMON42305

Source
ToetsingOnline

Brief title
IP chemo study

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
Ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Medische Oncologie
Source(s) of monetary or material Support: Ministerie van OC&W,Paul Speth fonds

Intervention

Keyword: Cisplatin, Ovarian Neoplasms, Pharmacokinetics, Predictive factors

Outcome measures

Primary outcome

Patient data

Patient data on age, tumor type, grade and stage, surgery type and outcome, I.P. chemotherapy dosing and toxicity, CA 125 and progression free survival (PFS) site of recurrence (intraperitoneal versus extraperitoneal), overall survival (OS) .

Immune Lab data

The immune cells will be phenotyped to determine their nature (T cells, regulatory T cells, natural killer cells, dendritic cells, Myeloid-derived suppressor cells or macrophages M1 and M2 type), cytokine secretion and their functionality. If possible, cells will be frozen down for future analysis. STAT protein activation status of these cells will be determined alongside. Concurrently, a peripheral blood sample will be taken (5x 10 ml peripheral blood in heparin tubes on day 1 and day 8 of each round before i.p. chemo; to a maximum of 300 ml/year) and subjected to the same flowcytometry analysis of immune cell numbers, activation state and cytokine secretion as described above.

Pharmacokinetic data:

6 ml of EDTA blood samples will be collected at 0, 15, 30, 60 min and at 2 h,

4 h, 8h, 16h, 24 h, 48hr and 72hr at the first i.p cycle of chemotherapy. to

assess the concentrations of cisplatin and paclitaxel in the peripheral blood

after IP administration.Also 3 ml intra-peritoneal fluid will be collected at

time points -30 min 0 min, 15 min, 30 min, 60 min, 2hr , 4hr, 8h, 24h, 48 and

72 hr after i.p. infusion of cisplatin and paclitaxel.

Secondary outcome

Not applicable.

Study description

Background summary

Intra-peritoneal (i.p) chemotherapy with cisplatin and paclitaxel is currently the most effective treatment for patients with FIGO stage III ovarian cancer, improving life expectancy from 50 to 66 months. The current most evidence based schedule is day 1 start with paclitaxel135mg/m2 in 24hours intravenously (i.v.), day 2: cisplatin 100mg/m2 i.p. and day 8 paclitaxel 60mg/m2 i.p. to be repeated every 3 weeks for 6 courses. The improvement in life expectancy is achieved despite the fact that almost 30% of the patients do not complete the planned 6 courses of chemotherapy, mainly due to its toxicity. These results indicate that for some patients less than 6 courses of chemotherapy are sufficient. In other words, several patients are receiving unnecessary treatment, which have an enormous effect on quality of life. Hence, there is an obvious need for a predictive biomarker that can be used to tailor this treatment to individual patients.
It*s becoming increasingly evident that the efficacy of chemotherapeutic intervention is, in part, dependent on the modulation of the immune system. On a molecular level this is due to the modulation of signaling pathways such as the STAT protein family by these drugs. STAT proteins play an important role during tumorigenesis as well in the maintenance of an immunosuppressive tumor microenvironment. We have recently shown that platinum compounds like cisplatin can block STAT protein signaling in the tumor microenvironment[1-3]. Subsequently immunosuppressive networks present in the tumor are down regulated. Concurrently, platinum chemotherapy can also boost the immune response by enhancing dendritic cell function. Furthermore, in a small retrospective study, the expression of STAT6 in tumor cells had both predictive and prognostic value for platinum chemotherapy.
Since ovarian cancer suppresses the immune system, it is worthwhile to assess

the effect of chemotherapy on the ovarian cancer cells and the immune system. Patients who are eligible for intra-peritoneal chemotherapy receive a port a cath (PAC)to infuse NaCl 0.9% and cisplatin and paclitaxel according to protocol into the intra-peritoneal cavity but also this device gives us the opportunity to aspirate intra-peritoneal fluid to monitor he tumor microenvironment, malignant cells and the immune system in the peritoneal cavity during chemotherapy.

The distribution of cisplatin and paclitaxel chemotherapy from the peritoneal cavity to the circulation is not known. According to the toxicity profile of these drugs with nephropathy, neuropathy, hearing loss and myelosuppression, they have to be distributed to the central circulation. Whether plasma levels of these drugs are conform intravenously infused drugs is currently unknown, as is the distribution of recurrences in and outside the abdominal cavity.

Study objective

Primary:
• In this project, we propose to study the use of this aspiration fluid from the intraperitoneal cavity as a biomarker for the efficacy of chemotherapy intervention.
The research questions for this study are:
• Monitor the effect of chemotherapy on intra-peritoneal tumor cells in the peritoneal cavity before and over the course of the intra-peritoneal chemotherapy regimen and if possible also after cessation of intraperitoneal chemotherapy when replacement with i.v. chemotherapy occurs.
• Monitor the effect of chemotherapy on immune cells present in the intra-peritoneal cavity over the course of the intra-peritoneal chemotherapy regimen.
• Correlate the presence and amount of tumor cells in peritoneal fluid with the debulking efficacy and CA 125 levels
Secondary:
• To determine the pharmacokinetics of cisplatin and paclitaxel when administered in the intraperitoneal cavity in the central circulation (plasma) as well as in the peritoneal fluid.

Study design

Prospective observational explorative study

Study burden and risks

For the patient no extra invasive actions are needed apart from the standard chemotherapy.
The only burden is that more blood will be sampled until a maximum of 432 ml

over a period of 18 weeks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Primary epitelial ovarían carcinoma FIGO stage III
Optimal primary debulking (tumor rests <=1cm)
WHO 0-2
Adequate hematological, renal and liver function tests, conform standard protocol for chemotherapy
Creatinine clearance >60 ml/min (Cockroft)
Bilirubin and/or transaminases < 1,25 UNL
WBC>= 3. 10^6/L en Platelets >= 100. 10^6/L

Exclusion criteria

Intestinal stoma proximal to the flexura lienalis
Sepsis postoperative after primary debulking
Extended intraperitoneal adhesions
Neurotoxicity grade >1
Previous chemotherapy for ovarian carcinoma
Symptomatic hearing loss
Age >70 years old
Haemoglobin < 6.0 mmol/L

Study design

Design

Study phase:	2
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-08-2016
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	22-01-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-06-2016

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL50438.091.15