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Intraperitoneal aerosolization of albumin-stabilized paclitaxel nanoparticles (Abraxane™) for peritoneal carcinomatosis – a phase I first-in-human study

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Abstract

Background: Nanoparticles hold considerable promise for aerosol-based intraperitoneal delivery in patients with carcinomatosis. Recently, results from preclinical and early clinical trials suggested that albumin-bound paclitaxel (ABP, Abraxane™) may result in superior efficacy in the treatment of peritoneal metastases (PM) compared to the standard solvent-based paclitaxel formulation (Taxol™). Here, we propose a phase I study of pressurized intraperitoneal aerosol chemotherapy (PIPAC) using ABP in patients with upper Gastrointestinal, breast, or ovarian cancer.

Methods: Eligible patients with advanced, biopsy-proven PM from ovarian, breast, gastric, hepatobiliary, or pancreatic origin will undergo three PIPAC treatments using ABP with a 4-week interval. The dose of ABP will be escalated from 35 to 140 mg/m² using a Bayesian approach until the maximally tolerated dose is determined. The primary end point is dose-limiting toxicity. Secondary analyses include surgical morbidity, non-access rate, pharmacokinetic and pharmacodynamic analyses, quality of life, and exploratory circulating biomarker analyses.

Discussion: ABP holds considerable promise for intraperitoneal aerosol delivery. The aim of this study is to determine the dose level for future randomized phase II trials using ABP in PIPAC therapy.

Trial registration: This trial is registered as EudraCT: 2017-001688-20 and Clinicaltrials.gov: NCT03304210.

Keywords: Abraxane, aerosol, albumin, carcinomatosis, intraperitoneal, pressurized intraperitoneal aerosol chemotherapy (PIPAC).

Introduction

The introduction of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion (HIPEC) has improved the outcome of patients with peritoneal carcinomatosis from GI and ovarian origin [1, 2]. However, a significant proportion of these patients are not amenable to surgery due to extensive and/or irresectable disease.

Recently, the technique of laparoscopic (pressurized) intraperitoneal (IP) aerosol chemotherapy (PIPAC) was introduced in clinical practice [3, 4]. During laparoscopy, chemotherapy is delivered as an aerosol, generated by a dedicated micropump connected to a high-pressure injector. Advantages of PIPAC include minimal patient discomfort, possibility of repeated delivery, potential to combine with systemic treatment, and possibility to assess pathological response of peritoneal disease by serial biopsies. A recent prospective cohort study in women with peritoneal carcinomatosis (84% ovarian cancer) showed that repeated PIPAC resulted in an objective response (histological regression after the first procedure) in 76%, a significant decrease in peritoneal cancer index, and a significantly decreased ascites volume [5]. Also, EORTC QLQ-30 + 3 scores for global physical health, nausea/vomiting, appetite loss, and constipation improved during therapy.

In theory, any cancer drug may be delivered IP as an aerosol. Because of their activity profile and molecular size, the taxanes are ideal candidates for IP

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administration. The potential of Taxol™ for IP administration is, however, limited by the local toxicity and potential of hypersensitivity reactions associated with the Cremophor EL™ component. Abraxane™ (Celgene) is a novel 130 nm, albumin-bound (nab™) nanoparticle formulation of paclitaxel (albumin-bound paclitaxel [ABP]) which has demonstrated activity in metastatic breast, pancreatic, and non-small-cell lung cancer [6]. Preclinical studies have demonstrated that IP administration of nano- and microsized formulations of paclitaxel results in superior antitumor activity against mouse ovarian cancer (OC) xenografts compared to intravenous administration [7]. In a recent study using an HIPEC model in the rabbit, peritoneal tissue concentrations after IP ABP were five times higher compared to IP Taxol [8]. IP catheter-based delivery of Abraxane was recently studied in a phase I clinical trial in advanced carcinomatosis patients [9]. The maximally tolerated dose (MTD) of IP nab-paclitaxel was140 mg/m^2; dose-limiting toxicities (DLTs) included grade 3 neutropenia resulting in treatment delay > 15 days, grade 3 abdominal pain, and grade 4 neutropenia > 7 days. Over the four-dose levels, there was a ~150-fold pharmacokinetic (PK) advantage (AUC_{ip}/AUC_{plasma}) with low intra-patient variability.

Based on the above considerations, we hypothesize that PIPAC with ABP is a rational strategy to test in patients with unresectable peritoneal carcinomatosis (PC) from ovarian, breast, or upper GI origin. Here, we propose a study protocol of a phase I dose-escalation study with several translational research end points.

Methods

General design

This is a multicenter, first-in-human phase I dose-escalation study to explore the safety of PIPAC using ABP in patients with unresectable peritoneal carcinomatosis.

End points

The primary end point of the study is the MTD of ABP, administered three times every 4 weeks using IP laparoscopy-assisted aerosolization (PIPAC).

Secondary end points include pharmacokinetic/pharmacodynamic analysis, pathological response rate, surgical morbidity and mortality of laparoscopy, quality of life at 2 and 6 months, and technical failure rate.

Inclusion criteria

Patients with advanced, biopsy-proven PC from ovarian, breast, gastric, hepatobiliary, or pancreatic origin. Concurrent systemic cancer treatment with a taxane is not allowed. Detailed inclusion and exclusion criteria can be found on clinicaltrials.gov/ct2/show/NCT03304210.

Experimental methods (Table 1)

Surgical procedure: Patients will undergo three PIPAC procedures with an interval of 4 weeks. This interval is chosen in anticipation of future randomized comparisons of systemic chemotherapy with or without concurrent PIPAC, which can be added in week 4 of commonly used systemic therapy regimens. Each procedure will consist of the following steps:

1. Exploration, peritoneal carcinomatosis index calculation, digital imaging of the entire cavity
2. Punch biopsies in each abdominal quadrant (left fossa, right fossa, left upper abdomen, and right upper abdomen), if disease is present
3. IP aerosol delivery of ABP; evacuation after 30 minutes using the closed circuit. No electrostatic precipitation is used.
4. Pneumoperitoneum is re-established and four additional punch biopsies taken, adjacent to the previous location. Biopsy sites are marked with a clip (only during first PIPAC).

Dose escalation of albumin-bound paclitaxel: Dose levels of ABP will be 35, 70, 90, 112.5, and 140 mg/m^2. The same dose will be used for all three treatments in the same patient. The estimated plasma half-life of ABP ranges from 13 to 27 hours.

Additional and translational end points:

- Pharmacokinetic analysis: Plasma samples (5 mL) will be collected at the start of nebulization and 15, 30, and 60 min and 1.5, 2, 4, 8, 12, and 24 h after each PIPAC procedure. Drug concentrations will be measured using ultra-performance liquid chromatography–tandem mass spectrometry. Tumor tissue samples in each abdominal quadrant (n = 4 punch biopsies, approximately 8–10 mm^3) will be taken at the end of aerosol delivery after each PIPAC procedure for tissue paclitaxel concentration analysis.
- Pharmacodynamic (PD) analysis: Tumor tissue samples (punch biopsies, approximately 8–10 mm^3) will be taken in each abdominal quadrant before (n = 4) and at the end (n = 4) of aerosol delivery after each PIPAC procedure. Standard histology and immunohistochemistry (caspase 3) will be performed on tissue biopsies.
- Plasma biomarkers of treatment response: Part of the plasma samples (5 mL) taken before surgery and at days 1 and 7 after each PIPAC will be stored for exploratory biomarker analysis (circulating tumor cells, circulating DNA, and extracellular vesicles).
- Quality of life: QLQ-C30 and Functional Assessment of Cancer Therapy-General (FACT-G) questionnaires will be taken 1 day before each PIPAC, 2 weeks after each PIPAC, and 2 and 6 months after the third PIPAC procedure.
- Postoperative pain score: Patients will be asked to score pain on a visual analog scale 1 day before each PIPAC and at 8, 12, and 24 h and 1 week after each PIPAC procedure.

Table 1: Overview of experimental interventions.

	Study period												
	Enrollment	Allocation								Postallocation			Follow-up
Time point	Preoperative	0 week	1 week	2 weeks	3 weeks	5 weeks	6 weeks	7 weeks	9 weeks	10 weeks	11 weeks	17 weeks	35 weeks
Enrollment													
Eligibility screen	x												
Informed consent	x												
Allocation		x											
Interventions													
PIPAC 1			x										
PIPAC 2						x							
PIPAC 3									x				
Assessments													
Blood sampling for toxicity		x	x			x			x				
Blood sampling for PK modelling			x			x			x				
Tumor biopsies for PK modelling			x			x			x				
Blood sampling for PD modelling		x	x	x		x	x		x	x			
Quality of life		x			x			x			x	x	x
Pain score		x	x	x		x	x		x	x			

Ethical approval

The study protocol was approved in its amended form by the Ethical Committee of Ghent University Hospital, which acts as the central Ethical Committee, on 6 April 2018 (ref 2017/0920). Approval by the Ethical Committee of the other participating centers is pending.

Statistical considerations

In order to minimize the sample size, a Bayesian approach with continual reassessment will be used [10]. Conservative a priori estimates of DLT (defined in Table 2) are used for initial simulation, resulting in a moderate pace of escalation: 35–35–70–70–90–90–90–112.5–112.5–112.5–140–140–140–140–140–140–140–140–140–140 mg/m^2. The maximal dose of 140 mg/m^2 is based on the finding that this was the MTD in the study of Cristea et al. [9]. The provisional sample size is therefore 20, but this is subject to recalculation.

Results and discussion

While IP drug delivery has been firmly established as a treatment option in patients with PC, clinical treatment has to rely on off-label use of drugs that were developed and approved for systemic treatment. Therefore, development of drugs or platforms that are specifically designed for IP delivery is a priority. Theoretically, nanobodies hold promise for IP delivery, due to their peritoneal retention and the possibility to incorporate a variety of targeted and untargeted payloads [11]. Albumin-based nanoparticles are approved for systemic treatment of cancer. It is rational to explore IP delivery of IP administration of albumin-bound particles. First, cancers such as ovarian and pancreatic cancers express high levels of secreted protein acidic and rich in cysteine (SPARC/osteonectin/BM40), an albumin-binding 42-kDa matricellular glycoprotein, the expression of which correlates inversely with outcome [12]. Also, macropinocytosis of ABP was shown to drive macrophage activation in mouse models, pointing to possible synergy with immunotherapy [13]. Other albumin-binding proteins and receptors that may mediate tumor accumulation of albumin-bound carriers include albondin (gp60), gp18, gp30, calreticulin, megalin, cubilin, heterogeneous nuclear ribonucleoproteins (hnRNPs), and the neonatal Fc receptor (FcRn) [14].

Preliminary data from animal models seem to confirm the potential of IP ABP administration. Coccolini

Table 2: Definitions of dose-limiting toxicity.

Overview of DLT	
Non-hematologic toxicity (CTCAE)	
Grade 3	Severe/medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.
Grade 4	Life-threatening consequences; urgent intervention indicated. Excluded: Fatigue, controllable nausea, vomiting, abdominal pain, and diarrhea.
Thrombocytopenia (CTCAE)	
Grade 4	$25–50 \times 10^3$/µl
Neutropenia (CTCAE)	
Grade 4	$0.5 –1 \times 10^3$/µl; lasting more than 7 days OR associated with fever
Failure to perform more than one PIPAC due to toxicity	
Surgical complication (Dindo-Clavien)	
Grade IIIB	Intervention under general anesthesia
Grade IV	Life-threatening complication (incl. central nervous system complications) requiring intensive care management
Grade IVa	Single-organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction (including dialysis)
Grade IVc	Death of a patient

and coworkers compared HIPEC with either ABP or cremophor-based paclitaxel in a rabbit model and found that ABP penetrated up to 0.63 mm in the (healthy) peritoneal wall, while the standard formulation was not detectable in the peritoneum [8]. We have recently demonstrated that IP ABP results in significant antitumor efficacy in a mouse xenograft model of peritoneal metastasis from ovarian origin (Carlier et al., manuscript in preparation).

These considerations prompted us to explore the feasibility and safety of PIPAC using ABP. Data from our lab show that ABP remains structurally intact after nebulization and after dilution (unpublished data). Systemic toxicity is expected to be limited, since Cristea et al., in a phase I trial of IP instillation of ABP for advanced carcinomatosis, found a significant pharmacokinetic benefit associated with IP delivery [9]. In order to limit the sample size, we opted for a Bayesian approach, which consists of continually reassessing the probability of toxicity based on the prior toxicity observed. Once the present phase I trial is completed, we plan to design randomized phase II trials in selected indications (e.g., recurrent, platinum-resistant epithelial ovarian cancer). In parallel, we will investigate the mechanisms of albumin-mediated nanoparticle transport mechanisms after IP delivery *in vitro* and *in vivo*.

Author contributions: WC, WW, and LVDS authored the manuscript. All authors have read and approved the final manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Availability of data: All anonymized source data will be made available by the principle investigator, upon request.

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