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# Pressurized intraperitoneal aerosol chemotherapy as an innovative approach to treat peritoneal carcinomatosis

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ABSTRACT

Peritoneal carcinomatosis (PC) is difficult to treat and many efforts have been made to identify effective and safe treatments. One hypothetical way to increase the efficacy of chemotherapy regarding tumor eradication or tumor control is to apply chemotherapeutic agents into the abdomen in the form of a pressurized aerosol, taking advantage of the physical properties of gas and pressure. This new approach for treatment of PC is based on the assumption that (1) intraabdominal application of chemotherapy under pressure will enhance tumor drug uptake and (2) aerosolizing and spraying chemotherapy will enhance the area of peritoneal surface covered by the drug, (3) resulting in an improved anti-tumor efficacy. Ex vivo and in vitro models have tested this approach and have demonstrated good peritoneal cavity coverage, deep peritoneal drug infiltration, and technical feasibility. Occupational safety of this procedure has also been established. First evidence in humans with peritoneal cancer from ovarian cancer, gastric cancer, colon cancer, appendiceal cancer, and pseudomyxoma peritonei has been obtained suggesting clinical antitumor activity and procedural safety of repeated pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin. We hypothesize that PIPAC can effectively treat PC and will hence become part of the surgical and chemotherapeutical treatment spectrum of this disease in the future.



## Background

Peritoneal carcinomatosis (PC) can occur as an isolated disease or secondary to other malignancies of the gastrointestinal, urinary, and genital tract such as colon, gastric, and ovarian cancer [1]. In women with ovarian cancer, for example, PC is found in 2/3 of cases at initial presentation and in the majority of women with recurrent disease [2]. PC is difficult to treat due to the large surface of the peritoneal cavity as well as poor vascularization of the peritoneum. These factors limit the potential of systemic chemotherapy to effectively eradicate PC. Despite these limitations, systemic intravenous chemotherapy with platinum compounds, taxanes, anthracyclines, gemcitabine, topotecan, and trabectedin in various combinations and sequences is the standard of care for women with PC. In women with recurrent ovarian cancer and PC, for example, the median survival rate after the diagnosis of ovarian cancer recurrence with PC is poor ranging between 4 and 15 months [2]. Also, the morbidity associated with repeated lines of systemic chemotherapy is substantial. For example, Kayl and Meyers cite nausea, emesis, alopecia, changes in taste, and fatigue as the most bothering symptoms in a review of systemic chemotherapy-related side effects [3]. These numbers may even be higher in geriatric cancer populations who make up around 50% of women affected by ovarian cancer as well as other cancers associated with PC [1,2]. Clearly, alternatives are needed to improve the efficacy and tolerability of PC treatments.

Intraperitoneal chemotherapy (IPC) may be a therapeutic alternative to systemic chemotherapy in patients with PC. IPC allows to directly target malignant cells which have spread throughout the peritoneal cavity. IPC has already been established as beneficial in some clinical settings. For example, in women with ovarian cancer after primary debulking surgery, adjuvant IPC with cisplatin and paclitaxel in combination with intravenous systemic chemotherapy has been demonstrated in randomized clinical trials and meta analyses of these trials to significantly prolong progression-free survival and to increase overall survival [4,5]. Although proven to be effective in the adjuvant setting, IPC has not been tested in the recurrent situation so far. The potential of IPC to improve survival in women with PC, however, may be high, given its potential to improve survival of patients with residual disease after initial surgery. In addition, in women with PC from colon cancer and pseudomyxoma peritonei (PMP), a multimodal

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treatment approach with cytoreductive surgery and IPC is considered the mainstay of treatment [6,7]. In a systematic review and meta-analysis of 15 studies, for example, McBride et al. report mean 3-year, 5-year, and 10-year survival rates of 77%, 76%, and 57%, respectively, in women with PMP treated with cytoreductive surgery and IPC [7]. However, combining cytoreductive surgery with IPC has a high morbidity and a considerable mortality. For example, Saxena et al. reported a 3% mortality rate and grade 3 and 4 morbidity rates of 23% and 22%, respectively, in a series of 145 women with PMP treated with cytoreductive surgery and IPC [8].

The potential of IPC to improve survival in women with PC from various primary cancers is restricted by pharmacological limitations such as poor drug distribution within the abdominal cavity and poor drug penetration into peritoneal nodules [9]. Therefore, it is reasonable to investigate new and innovative IPC concepts overcoming these limitations. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is such an innovative IPC concept.

## The hypothesis

There are many potential ways to improve the efficacy of IPC including dose escalation, hyperthermia, or combinations of chemotherapy and targeted therapy compounds. Another simple, cheap, and potentially effective way to overcome the pharmacokinetic limitations of IPC is to apply chemotherapy in the form of a pressurized aerosol. We hypothesize that applying chemotherapy into the abdomen as a pressurized aerosol (pressurized intraperitoneal aerosol chemotherapy; PIPAC) will enhance the effectivity of IPC by taking advantage of the physical properties of gas and pressure. This new therapy is based on the assumption that (1) intraabdominal application of chemotherapy under pressure will enhance tumor drug uptake and (2) aerosolizing and spraying chemotherapy will enhance the area of peritoneal surface covered by the drug. PIPAC allows to apply various aerosolized chemotherapeutic compounds under pressure via laparoscopy. In contrast to other IPC concepts such as hyperthermic intraperitoneal chemotherapy (HIPEC), PIPAC can be applied repeatedly thus increasing the potential to achieve local control of recurrent PC. Also, repeated applications via laparoscopy allow sequential tumor sampling thus enabling the treating physician to directly measure and document the histologic treatment response. This is an important aspect of PIPAC given the poor performance of computed tomography regarding PC assessment and scoring [10].

## Evaluation of the hypothesis

The hypothesis as outlined above has been evaluated in preclinical studies. In a literature search (PUBMED; search terms: PIPAC, intraperitoneal chemotherapy, peritoneal cancer, peritoneal carcinomatosis; search date: April 1, 2015), we identified four studies describing experimental evidence, methods, and pre-clinical applications of PIPAC. Of these, two studies described experimental in vivo and ex-vivo experiments [11,12] and two studies described methodological and occupational safety aspects of PIPAC [13,14]. Another four studies reported clinical outcomes in women with PC from colon, appendiceal, and ovarian cancer and PMP [13,15–17].

### *Preclinical applications of PIPAC*

As proof of concept, PIPAC achieved a superior distribution on the peritoneum and a better penetration into peritoneal nodules compared to conventional IPC in an ex vivo model [11]. In this experimental model, a nontoxic therapeutic agent (Dbait, ie noncoding DNA fragments) was aerosolized into a box containing diseased human peritoneum under a pressure of 12 mmHg $CO_2$. Dbait were coupled to cholesterol molecules to facilitate intracellular uptake, and to Cyanine (Cy5) to allow detection by fluorescence. In a control experiment, the same solution was applied to the other half of the sample using conventional lavage. Using this experimental approach, fluorescence was demonstrated within the tumor up to 1 mm depth in the therapeutic capnoperitoneum sample, but no uptake in the lavage sample. Intranuclear phosphorylation of H2AX was seen in the nebulized sample and no activity in the lavage sample. Detection of histone gamma-H2AX (phosphorylated H2AX) indicated activation of DNA-dependent protein kinase (DNA-PK) by Dbait, which has been shown to be the key step for sensitization to genotoxic therapy. In an in vivo experimental study using five pigs, PIPAC yielded a better distribution of a pressurized test dye within the abdominal cavity and a better penetration into the peritoneum compared to peritoneal lavage [12]. Specifically, the stained peritoneal surface was larger after pressurized aerosol application compared with peritoneal lavage, and staining was more intense. Hidden peritoneal surfaces as well as the anterior abdominal wall were only stained in the pressurized aerosol group and the outer aspect of the peritoneal membrane was immediately stained after pressurized spraying. Thus, PIPAC successfully improved both distribution and penetration of a test substance into the peritoneal cavity in a large animal model.

### *Methodological and occupational safety aspects of PIPAC*

The occupational safety of PIPAC has been tested to rule out staff hazard and exposure to chemotherapy compounds in the operating theatre. This was based on the assumption that delivering chemotherapy as an aerosol might result in an increased risk of exposure to health care workers, as compared with other administration routes. In order to test occupational safety aspects of PIPAC under standardized conditions, PIPAC was applied in simulation experiments as well as in two human patients using chemotherapeutic drugs (doxorubicin and cisplatin), and air contamination levels were measured under real clinical conditions. Air was collected on a cellulose nitrate filter with a flow of 22.5 $m^3$/h. To exclude any risk for health care workers, both procedures were remote controlled. Toxicological research of cisplatin was performed according to NIOSH 7300 protocol. Sampling and analysis were performed by an independent certification organization (DEKRA Industrial GmbH, Stuttgart, Germany). In these tests, no cisplatin was detected in the air (detection limit <0.000009 mg/$m^3$) at the working positions of the surgeon and the anesthesiologist under real PIPAC conditions [14]. Based on these results, PIPAC is in compliance with European Community working safety law and regulations. Workplace contamination remains below the tolerance margin. Based on these experiments, PIPAC can be used safely in the clinical setting if the conditions specified above are met. It has to be acknowledged, however, that these tests have only been performed with the chemotherapy compound cisplatin. Using other drugs may result in different exposures.

### *Preliminary safety and efficacy data*

The efficacy and safety of PIPAC has been assessed empirically in small case series of patients with PC. Four studies reported clinical outcomes in women with PC from colon, appendiceal, and ovarian cancer and PMP [13,15–17]. Another study evaluated quality of life according to the EORTC QLQ-30 questionnaire in 91 patients undergoing PIPAC [18]. Three ongoing prospective clinical trials were identified in the EudraCT and US National Institutes of

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