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Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) as an outpatient procedure

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Abstract

Background: Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is a drug-delivery method for patients with peritoneal metastasis (PM). The study objective was to investigate whether PIPAC is possible in an outpatient setting.

Methods: Data was extracted from the prospective PIPAC-OPC2 study (ClinicalTrials.gov NCT03287375). Patients with PM were treated by cisplatin and doxorubicin (PIPAC C/D), except patients with colorectal PM, who were treated by oxaliplatin (PIPAC OX). Patients were evaluated concerning the suitability for carrying out the PIPAC procedure in an out- patient setting. The preconditions for outpatient surgery were that the patient should be (1) freely mobilized, (2) adequately pain-relieved, (3) have untroubled urination and (4) without anxiety or discomfort caused by leaving the hospital.

Results: During the study period, 106 PIPAC procedures (79 PIPAC C/D, 27 PIPAC OX) were performed in 41 patients with gastrointestinal or ovarian PM. Ninety percent (37/41) of the patients were pretreated with systemic chemotherapy. Eight patients (20%) received bidirectional chemotherapy. Twenty-four percent (10/41) of the first PIPAC procedures were completed in an outpatient setting, which increased to 65% (13/20) in PIPAC no 3 ($p = 0.008$). In the PIPAC C/D cohort, 28% and 80% of the PIPACs were performed in the outpatient setting at PIPAC 1 and 3 respectively, contrasting to only 11% and 20% in the PIPAC OX group. No readmissions after outpatient care. Postoperative morphine administration was more frequent in the PIPAC OX group.

Conclusions: The PIPAC procedure can be performed in an outpatient setting. The critical component for success is pain control.

Keywords: complications, intraperitoneal chemotherapy, outpatient procedure, peritoneal metastasis, PIPAC

Introduction

Peritoneal metastasis (PM) is a common evolution of abdominal cancers and is associated with a poor prognosis in the absence of aggressive multimodal therapeutic approaches. Systemic chemotherapy is frequently practiced but with questionable efficacy in patients with PM and only a minority of affected patients is eligible for cytoreductive surgery [1–3]. Research focus on alternative therapeutic approaches in patients with PM is warranted, especially in light of the relative chemo resistance towards systemic chemotherapy in PM. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) has shown up as a novel variant of intraperitoneal chemotherapy (IPC), using repeated laparoscopies to deliver chemotherapy compounds in the form of a pressurized aerosol into the abdomen [4–6].

A recent systematic review of the literature described the available evidence from experimental and clinical studies related to PIPAC in all indications [7], while another review focused on PIPAC directed therapy in ovarian cancer patients [8]. The authors concluded that treating PM with PIPAC is feasible, safe, and efficacious based on experimental studies, controlled

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clinical phase I and II trials and numerous retrospective cohort studies.

Pivotal considerations in the palliative management of advanced GI cancer stages are to offer treatments that are not only feasible and safe, but also effective, minimally toxic, delivered at a reasonable cost and with maintained or at the best improved quality of life (QoL). Most importantly, new and innovative treatment strategies should not remove the opportunity for the patient to spend most of his or her time together with family members and friends outside the hospital environment. In this perspective, aspects on outpatient interventions in the field of IPC regimens have to be explored. The objective of the present study was to evaluate and describe the possibility of performing PIPAC as an outpatient procedure at a tertiary referral center.

Materials and methods

Data was extracted from the ongoing, prospective PIPAC-OPC2 study (ClinicalTrials.gov identifier NCT03287375) [9]. Patients with an age > 18 years with gastrointestinal or ovarian cancer and clinical or radiological evident PM and a maximum of one extra-peritoneal metastasis were discussed at a dedicated PIPAC multidisciplinary tumor conference (MDT). Based on the in- and exclusion criteria (see below), patients were scheduled for PIPAC treatment. The Department of Surgery took care of the intra- and perioperative patient management and follow up in close cooperation with the Department of Oncology, which was in charge of all chemotherapy related issues. Following the MDT, the patient received oral and written information where after written informed consent was obtained.

A series of three PIPAC procedures were planned every 4–6 weeks (6–7 weeks, if combined with systemic chemotherapy in a bidirectional treatment strategy). Preoperative blood tests were performed, to rule out any contraindications for surgery, anesthesia or administration of chemotherapy. Criteria for entering into the study were: histological or cytological verified gastrointestinal-, ovarian- or primary peritoneal malignancy (based on tissue from the primary tumor and/or its metastases). Eastern Cooperative Oncology Group (ECOG) performance status should be 0–1. Ovarian cancer patients had to be platinum resistant and treated by at least one line of chemotherapy for platinum resistant disease. Moreover, the patients should not be candidates for cytoreductive surgery and HIPEC.

Exclusion criteria were: symptomatic small bowel obstruction or previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones. A history of allergic reaction to platinum containing compounds or doxorubicin, renal impairment (GFR < 40 mL/min, Cockcroft-Gault Equation), myocardial insufficiency (NYHA class > 2), impaired liver function (bilirubin $\geq 1.5 \times$ UNL (upper normal limit)) or hematological dysfunction (ANC $\leq 1.5 \times 10^9$/l and platelets $\leq 100 \times 10^9$/l) were also considered contraindications for PIPAC directed treatment.

Patients were, at the time of enrolment, evaluated concerning the suitability for carrying out the PIPAC procedure in an outpatient setting. The preconditions for outpatient surgery were that the patient should be: (1) freely mobilized, (2) adequately pain-relieved, (3) have untroubled urination and (4) without anxiety or discomfort caused by leaving the hospital. Finally, an authorized person should be present at home during the first 24 hours after the procedure.

PIPAC procedure

All PIPAC procedures were performed laparoscopically using two standard balloon trocars where the infusion of normo-thermic CO_2 maintained an intraabdominal pressure of 12 mm Hg. To reduce the risk of access lesions, a percutaneous ultrasound was performed at the start of each procedure. Following standard prophylactic antibiotics, PIPAC was carried out by using doxorubicin 1.5 mg/m^2 body surface in 50 mL NaCl 0.9% and cisplatin at a dose of 7.5 mg/m^2 body surface in 150 mL NaCl 0.9%. In patients with PM of colorectal origin, PIPAC was performed with oxaliplatin 92 mg/m^2 in 150 mL dextrose. Using a CE-certified nebulizer (CapnoPen, Gothia Medical, Billdal, Sweden) and a standard intravenous high-pressure injector (MEDRAD® salient dual contrast injector, Bayer HealthCare, Leverkusen, Germany), chemotherapy was installed at a rate of 30 mL/min with a maximum pressure of 200 pressure per square inch (PSI). After the installation of chemotherapy, a steady state was kept for 30 minutes, thereafter the intraabdominal air was evacuated in a closed system and the patient was closed according to departmental guidelines. The skin incisions were infiltrated with 20 mL of local anesthesia. Postoperative pain was relieved by paracetamol (1 g × 4) and on-demand ibuprofen or morphine. The pain situation was evaluated on a visual analog scale (VAS) from 0 to 10. In the case of a VAS score of > 3 the patients were informed to take ibuprofen and in case of VAS > 6 morphine was mandated. Postoperative nausea and vomiting (PONV) were minimized by perioperative dexamethasone and on-demand metoclopramide or ondansetron.

In April 2018, the standard PIPAC (as described above) was changed to ePIPAC [10] based on correspondence with the majority of PIPAC centers in Europe. During the ePIPAC procedure, the aerosolized chemotherapy is charged by electrostatic precipitation. Using the CE certified Ultravision generator (Ultravision, Alesi Surgical Ltd., UK), electrostatic precipitation has been routinely used at a standard laparoscopy for clearing surgical smoke but may also be used to charge aerosol particles during PIPAC, thus resulting in clearance of the therapeutic aerosol within a few seconds Following intraperitoneal delivery of chemotherapy, electrostatic precipitation was performed for (at least) one minute (or until the aerosol had been cleared completely by visual inspection). The patients were exsufflated immediately after one minute of electrostatic precipitation. No other changes to the entire pre-, per- and post-PIPAC setup were made.

After the procedure, patients were transferred to a recovery room and after a few hours, a general evaluation of the patient's general conditions and attitudes towards discharge from the hospital, already at the same day, were assessed and evaluated. Based on the considerations detailed above, the background concept was, that all patients should be treated in an outpatient setting, and they were given access to the Departments telephone hotline in case of questions or problems [11].

Following every PIPAC procedure, the patients were contacted by the principal investigator to bring information about histological/laparoscopic response, and ensure that the patient was ready for the

next PIPAC procedure, but also to identify any complications or adverse events related to the procedure according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). Follow-up continued until the PIPAC treatment had been ceased or the death of the patient.

If PIPAC treatment was discontinued, the patient received standard treatment or best supportive care, based on performance status and comorbidity.

Statistics

Values are given as means or medians where appropriate. Comparisons were performed using a Fishers exact test or χ^2-test, p-values were two-tailed and a p-value of 0.05 was considered statistically significant. The statistical software Stata, version 13 (Stata Corp, TX, USA) was used for statistical analyses.

Ethics

This study was conducted according to a predefined protocol and the Declaration of Helsinki, and it follows the ICH-GCP recommendations for good clinical practice and has been approved by the Regional Scientific Ethical Committees for Southern Denmark (IRB S-20,160,100) and the Danish Medicines Agency (2,016,083,464). Oral and written consent from participants were mandatory. ClinicalTrials.gov identifier NCT03287375, European Clinical Trials Database (EudraCT) number 2016–003394–18.

Table 1: Baseline characteristics.

Variable	Value
No. Patients	41
PIPAC C/D	32
PIPAC OX	9
Age, years (range)	61 (34–80)
Female/male	26/15
Palliative chemotherapy	37
1 line	23
2 lines	10
> 2 lines	4
Bidirectional chemo	8
Primary tumor	n
Gastric/GEJ	13
Colorectal	8
Ovarian	8
Pancreas	7
Other	5
Primary tumor resected	19

C/D, cisplatin/doxorubicin; GEJ, gastro-esophageal junction; OX, oxaliplatin; PIPAC, Pressurized Intraperitoneal Aerosol Chemotherapy.

Results

Patients were included from December 2016 to September 2018 and the last PIPAC procedure was completed in September 2018. During the study period, 41 patients with gastrointestinal or ovarian PM were treated with a total of 106 PIPAC procedures (median = 3 per patient, range 1–6) (Tables 1 and 2). In total 90% (37/41) of the patients were previously treated by palliative chemotherapy, whereas eight patients (20%) received bidirectional chemotherapy, with a wash out period of 2 weeks from systemic chemotherapy to PIPAC, and 1 week from PIPAC to systemic chemotherapy.

Among the 106 procedures, 79 were PIPAC C/D and 27 were PIPAC OX. The median procedure time dropped between the index and subsequent PIPAC procedures (Table 2). Twenty-nine patients had two PIPACs and 20 patients a third procedure. Out of these 41 patients, 10, 13 and 13 patients had their first, second and third PIPAC completed as an outpatient procedure. Twenty-four percent of the index PIPACs were completed as an outpatient procedure, which increased to 65% after PIPAC no 3 ($p = 0.008$). When the option of completing the treatment as outpatient surgery was studied by the type of chemotherapy administered, only a minority of patients given OX were able to follow this management strategy (Table 2). This contrasted sharply to the C/D treatment cohort, where 28% of the first PIPACs were done as an outpatient procedure and 80% of the third PIPAC. A substantial difference was observed in the requests for morphine to control pain, where the OX patients more often required similar compounds (Table 2). This posttreatment profile diverged from the fairly similar morphine use among the different patient groups in the preoperative situation (data not shown).

Therapy related adverse events are detailed in Table 3. One patient developed small-bowel obstruction three weeks after the second PIPAC procedure (CTCAE grade 4), one lethal outcome was registered in a patient who succumbed following cholangitis due to biliary stent dysfunction, which was considered unrelated to the PIPAC treatment as such. Otherwise minor adverse events were registered particularly so in those allocated to the outpatient treatment strategy, where no grade ≥ 3 events (i.e. no re-admissions) were reported.

Table 2: Procedure related data.

Variable		Value	
No. PIPACs		106	
PIPAC C/D		79	
PIPAC OX		27	
PIPACs/pt, median (range)		3 (1–6)	
Median procedure time, minutes (range)			
PIPAC 1 (n = 41)		96 (34–150)	
PIPAC 2 (n = 29)		85 (52–118)	
PIPAC 3 (n = 20)		82 (22–109)	
Length of stay, all patients			
	0 days	>0 days	
PIPAC 1	10 (24%)	31 (76%)	
PIPAC 2	13 (45%)	16 (55%)	
PIPAC 3	13 (65%)	7 (35%)	p = 0.008
Length of stay, PIPAC OX			
	0 days	>0 days	
PIPAC 1	1 (11%)	8 (89%)	
PIPAC 2	1 (13%)	7 (87%)	
PIPAC 3	1 (20%)	4 (80%)	
Length of stay, PIPAC C/D			
	0 days	>0 days	
PIPAC 1	9 (28%)	23 (72%)	
PIPAC 2	12 (57%)	9 (43%)	
PIPAC 3	12 (80%)	3 (20%)	p = 0.002
Morphine administration after PIPAC			
	PIPAC C/D	PIPAC OX	
PIPAC 1	10 (31%)	6 (66%)	
PIPAC 2	5 (23%)	4 (50%)	
PIPAC 3	1 (6%)	1 (17%)	

Unless otherwise stated, the number of patients in each group is shown. C/D, cisplatin/doxorubicin; OX, oxaliplatin; PIPAC, Pressurized Intraperitoneal Aerosol Chemotherapy; pt, patient.

Table 3: Complications after PIPAC according to CTCAE (version 4.0).

	CTCAE grade				
PIPAC	1	2	3	4	5
All patients					
1	8	18	2	0	1
2	7	5	3	1	0
3	8	4	0	0	0
Outpatients					
1	3	3	0	0	0
2	4	2	0	0	0
3	4	1	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events; PIPAC, Pressurized IntraPeritoneal Aerosol Chemotherapy.

Discussion

Obviously, a substantial proportion of PIPAC procedures in patients with PM, of abdominal cancer origin, can be completed as an outpatient procedure. This is important since hitherto this therapeutic concept has been completed only as a traditional in hospital treatment with a median hospital stay of three days [5, 12–15]. The present PIPAC study also reiterated the high safety profile, based on a total of 106 PIPAC procedures in 41 patients. The adverse events and surgical complications were mostly mild, transient and self-limiting. None of the patients had systemic side-effects apart from mild PONV. Postoperative adverse events were predominantly CTCAE grade 1–2 abdominal pain, nausea, constipation and urinary retention. CTCAE grades 3–5 were described in 7 of 106 procedures which reside in the lower part of the ranges (0–37%) presented in the literature, with highest rates described in a study that combined PIPAC with CRS [16] and in a study on gastric peritoneal metastases [17]. One fatal outcome was caused by biliary obstruction and stent dysfunction, without a direct causative relationship with the PIPAC procedure. Repeated PIPAC applications were possible in 29 of patients (71%), which have been reported to vary between 38% and 82%.

The main objective of the present study was to explore the magnitude to which these patients could be managed in an outpatient setting, with the obvious inborn advantages in the form of empowerment and health economic consequences for each individual patient. An expanding proportion of patients could be managed accordingly, reaching 80% of the C/D patients allocated for the third PIPAC session. This experience contrasted sharply to the outcome obtained in patients given OX, where only 20% of those submitted to a third session could be completed in the outpatient setting. In fact, only one patient treated by PIPAC OX throughout the study period was able to complete the treatment in the outpatient setting.

As the number of patients was limited, and based on the different size of the two groups, data from this heterogeneous study population should be interpreted with caution. However, looking at the difference in postoperative morphine demand between the two groups, it seems obvious, that PIPAC OX lead to more pain, which was probably the main reason why PIPAC OX patients were less prone to follow the outpatient therapeutic concept. As the number of patients who needed morphine after PIPAC in the PIPAC OX group was reduced throughout the course of therapy (non-significant p = 0.22), one could

assume, that the pain response to oxaliplatin was attenuated, but in four of six patients who completed three rounds of PIPAC OX, the dose of chemotherapy was reduced to 75% due to grade 2 post-procedural pain at PIPAC 1. As the entire setup in PIPAC C/D and PIPAC OX is identical apart from the administered drugs, the different pain response to PIPAC is probably drug or dose dependent [18]. Oxaliplatin is given at a 10 times higher dose than cisplatin, and as most patients report pain relief by dose reduction of oxaliplatin, the pain response is presumably dose dependent. Larger comparative datasets are needed before reconsidering the optimal dose of oxaliplatin, and two dose-escalation studies are ongoing (ClinicalTrials.gov Identifier: NCT03172416 and NCT03294252).

Despite the ambition to follow the outpatient strategy in all patients, it seems unclear why not more than 28% of the C/D patients were initially managed accordingly, a figure which profoundly changed after the ensuing sessions. This may reflect an inborn reluctance or limited experience by the staff taking the final decision in each individual patient. More likely, however, the patients' anxiety and concerns towards a new procedure were reduced throughout therapy, as they learned the lenient nature of PIPAC directed treatment. Twenty patients were treated by three PIPACs, and probably patient selection also influenced on the increasing number of patients, that were eligible for outpatient care at the third PIPAC.

The implementation of reforms to facilitate and disseminate outpatient surgery is an ongoing process. While overall rates of outpatient surgery have nearly doubled in the past two decades [19], it remains unknown whether this growth has been consistent across diverse surgical disciplines. Advances in anesthesiology (e.g. improved local and regional anesthesia) and the advent of minimally invasive surgical techniques (e.g. laparoscopy and endoscopy) have increased the safety and palatability of ambulatory procedures for patients [20]. In the clinical setting of palliative medicine for patients with advanced GI cancer the benefits of outpatient treatment have particular dimensions. Moreover, few data describe the distribution of outpatient surgery across care settings, including procedures performed in hospital outpatient departments and ambulatory surgery centers. Accordingly, and in view of these considerations, it can be argued that further streamlining of the organization carries the potential to offer even more PIPAC patients to have their treatments on an outpatient basis. Moreover, the obvious need for focused and/or alternative pain management strategies in patients offered certain cytotoxic regimens, mandates search for alternative pain control options or administration formulas.

In conclusion, further documentation is offered to show the safety and feasibility of PIPAC. Noteworthy was that a substantial proportion of PIPAC procedures in patients with PM can be completed as an outpatient procedure. The critical component for success is pain control. Larger study populations are needed to validate, whether PIPAC OX finally leads to more pain than PIPAC C/D. The optimal design for PIPAC directed therapy in an outpatient setting needs to be better defined.

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