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II.g) PIPAC

F01
PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IS EFFECTIVE IN PERITONEAL CARCINOMATOSIS OF PANCREATICOBILIARY ORIGIN

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Objectives

Data on effectiveness of PIPAC in patients with peritoneal carcinomatosis of pancreaticobiliary origin is scarce. We herein present further proofs of treatment efficacy in these subset of patients.

Methods

Repetitive PIPAC treatment with Cisplatin 7,5 mg/m² and Doxorubicin 1,5 mg/m² body surface area every 6 weeks and prospective data collection. Documentation included microscopic regression analysis, median overall survival and treatment-related adverse events.

Results

Nine patients with a median age of 61 years (range, 51–78 years) were included. Four patients suffered from peritoneal carcinomatosis of pancreatic adenocarcinoma and five patients of cholangiocarcinoma. In total 19 cycles of PIPAC were performed and the mean number of PIPAC cycles was 2 (range, one to four). Complete tumor regression was found in four patients and major regression in one patient. Median overall survival after the first PIPAC cycle was 33,2 weeks and 8 of 9 patients are still alive after a median follow-up of 280 days. There were no CTCAE grade 3 or 4 complications.

Conclusion

PIPAC is an innovative and appealing treatment option in patients with peritoneal carcinomatosis of pancreaticobiliary tumors ineligible for CRS and HIPEC. In almost 50% of the patients histological regression can be induced. Further studies are warranted to further elucidate treatment efficacy.

F02
IMPLEMENTATION OF A PIPAC PROGRAM IN AN OPERATING ROOM WITHOUT LAMINAR AIRFLOW: IS THE PROCEDURE SAFE FOR THE SURGEONS AND THEIR CO-WORKERS?

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Objectives

Even if standardized safety measures are now well established for pressurized intraperitoneal aerosol chemotherapy (PIPAC), the safety of the procedure is often questioned by the surgeon's co-workers when newly implemented in an operating room as it may increased the risk of exposure to cytotoxics for health care workers. Only one published study in 2013 confirmed the absence of detection of cytotoxics in the air at the working positions of the surgeon and the anesthesiologist but no data exists on cytotoxic dosages on environmental items in the operating room without a laminar airflow. Furthermore, surgical teams that want to implement a PIPAC program in their unit are not necessarily equipped with laminar airflow operating rooms. The objective of the study was to ensure the safety of PIPAC for surgeons and co-workers for newly implemented procedures in an operating room without laminar airflow.

Methods

Twenty-six samples with cellulosic wipes on surgeon and co-workers' environmental items and 5 specific polytetrafluoroethylene air-filtered collections were randomly performed for the first 2 cisplatin/doxorubicin-based PIPAC procedures in Strasbourg University Hospital, Strasbourg, France. PIPAC were performed according to previously described safety protocol but without a laminar airflow and with an additional plastic cover and smoke evacuation device. Sampling and analyzes were performed by 2 accredited independent certification organizations.

Results

Air measurement were performed between 154 and 330 minutes around the surgeons, the nurses, the anesthesiologists' induction room, the operating room where PIPAC were performed and a control operating room without PIPAC. Wipe samples were taken on the floor, the injector, the cytotoxic component, the vacuum grid, inside the protective plastic cover and on surgeon's and nurse's hoofs, gloves (2 pairs) and hands. All air measurements were negative for cisplatin and doxorubicin. Only one wipe sample out of 26 was positive for cisplatin (3.8%). The only positive sample was on the first surgeon's pair of gloves but dosages on the surgeon's second pair and hands were negative.

Conclusion

Implementing a new PIPAC program is a source of questionable safety for surgeon's co-workers. When performed in approved security conditions, even without laminar airflow, PIPAC seems harmless for surgeons and their co-workers with very limited risks of exposure to cytotoxics.

F04

PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) WITH OXALIPLATIN, CISPLATIN AND DOXORUBICIN IN PATIENTS WITH PERITONEAL CARCINOMATOSIS: ANALYSIS OF AN OPEN-LABEL, SINGLE-ARM, PHASE II CLINICAL TRIAL

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Objectives

PIPAC is an innovative approach to peritoneal carcinomatosis (PC) that applies chemotherapic drugs into peritoneal cavity as an under pressure air-flow. It improves local bioavailability of cytostatic drugs as compared with conventional intraperitoneal chemotherapy. Aim of this study is to prove feasibility, efficacy and safety of this new approach; hereinafter the analysis of this phase II trial.

Methods

Patients included for the analysis underwent at least 2 PIPAC procedures. The primary endpoint was the Overall Response Rate according to RECIST criteria. Secondary significant endpoints were clinical tumor response using FDG-PET, tumor regression on histology, PC Index improvement and quality of life. Safety and tolerability has been assessed by collection of adverse events, according to the CTCAE 2.

Results

Between June 2015 and December 2017, 171 single-port PIPAC procedures in 82 patients presenting PC from different primary tumors, not eligible for surgery±HIPEC, were performed. 63 patients were enrolled. 40 patients were eligible for analysis. 9 patients reported a disease stability, 6 a partial response; some patients didn't perform radiological re-evaluation. 20 patients were undergoing systemic chemotherapy (sCT) with a wash-out interval of at least 2 weeks before and 1 week after each PIPAC. Clinical tumor response according to PERCIST criteria resulted to be a not reliable tool considering the mucinous histology of some patients and the lack of sensitivity in assessing the PC. Tumor regression on histology was evaluated after 2 PIPAC procedures according to the Peritoneal Regression Grade Score: a PRGS Score 1, 2 and 3 was recorded in 5, 1 and 18 patients respectively. CTCAE grades 1 and 2 were observed after 3 and 5 procedures, respectively, for abdominal pain and nausea. Renal and hepatic functions were not impaired; no cumulative renal toxicity was observed after repeated PIPAC procedures. There were no treatment-related deaths. Global physical health scores and pain improved during therapy.

Conclusion

Single-port PIPAC resulted to be feasible, safe and easy to perform; the combined treatment (PIPAC+sCT) doesn't induce hepatic and renal toxicity. This new approach as well as being ethically accepted, may be an useful strategy for patients not eligible to radical surgery, presenting extra-peritoneal disease or at high risk of developing it. An amendment of the protocol with a phase I study part is currently ongoing.

F05

SAFETY AND FEASIBILITY OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC). SUGGESTIONS FROM INITIAL EXPERIENCE ON NON-RESECTABLE GASTROINTESTINAL OR GYNECOLOGICAL PERITONEAL CARCINOMATOSIS

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Objectives

The main objective of this research was to evaluate safety and feasibility of PIPAC in a prospective observational study. The aim of this paper is to share our initial experience of PIPAC in patients with non-resectable PC of gastrointestinal or gynecological origin pointing out suggestions on patient selection.

Methods

Patients with non-resectable gastrointestinal or gynecological PC presenting to the Foundation Policlinico Universitario A. Gemelli (Rome, Italy) were prospectively enrolled from January 2016. Patients with recurrent gastrointestinal PC after cytoreductive surgery (CRS) or CRS plus HIPEC, patients with synchronous or metachronous non-resectable gastrointestinal PC who underwent at least one line of chemotherapy and patients with platinum-resistant gynecological recurrent PC who underwent CRS plus adjuvant therapy were included. PIPAC was performed with the administration of cisplatin (7.5 mg/m2) and doxorubicin (1.5 mg/m2) for gastric cancer, of oxaliplatin (92 mg/m2) for colon cancer and cisplatin (7.5 mg/m2) for gynecological cancer. Data on 30-day morbidity and mortality were collected. This study was approved by the Ethical Committee of our Institution.

Results

We enrolled 26 patients that underwent 44 procedures (range: 1–4 per patient). Forty-eight PIPAC were planned but in 4 cases it was not performed as the abdominal access was not feasible due to adhesions or unexpected disease extension. During the procedure, 2 (4,5%) intestinal perforations occurred among the gynecological patient population who underwent previous extended CRS; one of these patients died of sepsis. During the first postoperative month two patients presented with intestinal obstruction and were conservatively managed, and two death occurred: one patient died due to a cardiac event and the other because of liver failure.

Conclusion

Based on our initial experience, PIPAC is a not-devoid surgical risk procedure in patients previously receiving extended surgery for non-resectable gastrointestinal or gynecological PC. The establishment of a PIPAC-dedicated team composed by surgeons experienced both in the treatment of PC and laparoscopy is needed. An accurate preoperative patient selection through a clinical and radiological evaluation may reduce the risk of unsuccessful laparoscopic accesses, laparoscopic entry-related injury and an unexpected insufficient laparoscopic working space for chemotherapy administration.

F06

PRELIMINARY CLINICAL PIPAC EXPERIENCE IN A FRENCH HIPEC EXPERT CENTER

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Objectives

PIPAC (pressurized intraperitoneal aerosol chemotherapy) is a new intraabdominal technique to approach non resectable peritoneal carcinomatosis. PIPAC can be performed alone or in alternation with systemic chemotherapy in order to increase the effectiveness of tumor regression. We describe our initial experience

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performed in expert HIPEC (hyperthermic intraperitoneal chemotherapy) French center to proof safety and feasibility of PIPAC.

Methods

Between 2016 and 2018, PIPAC was proposed to 34 consecutive patients affected by digestive, ovarian, peritoneal and mammalian carcinomatosis diagnosed radiologically or by laparoscopy. Eighteen (53%) patients have already had primitive cancer removal. All patients have received at least one line of chemotherapy. Initially we proposed PIPAC to palliative patients with ascites, abdominal discomfort or diffuse peritoneal carcinomatosis non eligible for cytoreductive surgery. In last patients we associated PIPAC to systemic chemotherapy to potentiate tumor regression and lead patients to HIPEC. Patients were supposed to have six weeks between each PIPAC procedure for a total of three. Procedures were performed with two 10 mm trocarts and peritoneal biopsies were always performed to evaluate microscopic tumor regression. Cytology was performed when ascites was found. When no clinical postoperative improvement or quick tumor progression was found, treatment was stopped prematurely. Chemotherapies used were Oxaliplatine or Carboplatine and Doxorubicine depending on the cancer origin.

Results

In 4 (11.7%) patients PIPAC was not possible due to intraabdominal adhesions and impossibility to perform a pneumoperitoneum. One death occurred in the first 30 postoperative days due to tumor progression. Unique major complication was a perioperative pneumothorax treated by a pleural drainage. Two of thirteen patients receiving Oxaliplatine had postoperative abdominal pain which needed more drugs assumption and longer hospitalization. Two patients after three procedures underwent HIPEC. Four patients that had at least two PIPACs had last biopsies showing an increased tumor regression.

Conclusion

PIPAC is a safe and feasible procedure that can be performed in patients with peritoneal carcinomatosis not eligible for surgery to reduce tumor invasion or for palliation to reduce symptoms. Contraindications are bowel occlusion and multiple intraabdominal adhesions.

F07

PLATINUM-INDUCED ANAPHYLACTIC SHOCKS, POST PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC), FIRST LITERATURE REPORT

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Objectives

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) shows encouraging results for patients with unresectable peritoneal metastasis (PM). Several reports demonstrated the safety of the procedure combined with systemic chemotherapy, with a low rate of complications. The aim of this study is to report platinum-induced anaphylactic shocks (PIAS) during PIPAC procedures.

Methods

All patients who underwent PIPAC for non-resectable PM in Lyon Sud University Hospital were included in a prospective institutional database. All patients who have presented a PIAS after PIPAC were included in our analysis.

Results

One hundred thirty-two patients underwent 383 PIPAC procedures between December 2015 and December 2017. Oxaliplatin, and Cisplatin-Doxorubicin's PIPAC protocols were used in 71 and 312 PIPAC procedures respectively. Four patients (3%) developed a PIAS. Two patients (2.8%) after administration of aerosolized Oxaliplatin and two patients (0.6%) after Cisplatin-Doxorubicin protocol. PIAS occurred during the 6th PIPAC procedure with cisplatin-doxorobicin protocol and during 2nd and 3rd procedure with Oxaliplatin. Three events appeared within 15 minutes and one event occurred 50 minutes following nebulization. All the PIAS have been managed successfully without any complication.

Conclusion

This is the first report of PIAS after PIPAC. The physician must constantly keep this infrequent but life-threatening complication in mind, especially after repeated PIPAC administration or previous platinum-based systemic chemotherapy.

F08

PHARMACOKINETIC STUDY AND SAFETY OF PACLITAXEL IN PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) IN SWINE

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Objectives

Peritoneal carcinomatosis is a miserable disease with a disappointing response to systemic chemotherapy. PIPAC is a promising technique of administering chemotherapeutics directly to the peritoneum. Here, we aim to investigate the pharmacokinetics and short-term safety profile of PIPAC paclitaxel in a swine model to provide pilot data as a basis for future Phase I/II clinical trials.

Methods

PIPAC paclitaxel is administered in pigs at the starting dose of 60 mg/m2. This is followed by intravenous (IV) paclitaxel administration of the same dose on Day 7 to provide a control for pharmacokinetic comparison in the same animal. We plan to investigate 3 dose levels, with 3 pigs for each dose level.

Safety and toxicity is evaluated by daily clinical assessment of the pig as well as by blood counts and biochemistry. Ten blood samples are collected at 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 24, 48 hours for pharmacokinetic study after PIPAC. This is repeated after IV administration. The pig is euthanised after the last blood collection on day 9. The serum concentration of paclitaxel is determined by a well validated LC-MS/MS method. Pharmacokinetic analysis is then performed using non-compartmental analysis.

Results

As of April 25 2018, 5 pigs have undergone trial procedures. While all subjects remained clinically well, neutropenia on Day 7 was observed in all 3 pigs at the starting dose of 60 mg/m2 (absolute neutrophil count [ANC] 0.011–0.704 K/uL). The second dose level 30 mg/m2 was less myelosuppressive (ANC 1.33–2.89 K/uL).

There is an approximate 2-fold difference in Cmax and AUC between these 2 dose levels of paclitaxel when administered via PIPAC. The mean maximum concentrations (Cmax) was 45.9 ng/mL (34.9–56.7 ng/mL) compared with 26.2 ng/mL (21.0–31.5 ng/mL) and the mean AUC was 663.6 ng/mL*h and 313.6 ng/mL*h at the doses of 60 mg/m2 and 30 mg/m2 respectively. Compared to 1-hour IV infusion, the mean Cmax of PIPAC paclitaxel is 10 fold less than that of IV infusion. However, the difference between AUCs is less than 3.5 times.

Conclusion

This study extends our knowledge of peritoneal drug absorption when delivered via the novel PIPAC technique. The study is still ongoing. Further detailed analysis with data from more subjects treated at different dose levels will help define the appropriate drug dose for clinical use.

F09
PHARMACOKINETIC OF PLATIN SALT DURING PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC)

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Objectives

PIPAC is an innovative therapy *(Alyami M et al., Eur J Surg Oncol. 2017;43:2178–2183 Solass W et al., Ann Surg Oncol. 2014;21:553–559)* suitable patients with a high PCI and/or non-resectable peritoneal carcinomatosis. The tissue penetration is deeper with the aerosol than with a liquid, as done in HIPEC *(Minchinton AI et al., Nat Rev Cancer. 2006;6:583–592; Ferron G, et al. Cancer Chemother Pharmacol. 2008;62:679–683)* or during intravenous chemotherapy. The aim of the study is to analyze the patients pharmacokinetic of the platinum drugs in blood and peritoneal comparing to tissue penetration and peritoneal absorption.

Methods

Blood samples, peritoneal fluid samples and peritoneal biopsies were obtained from T0 to T240 mn after standardized PIPAC procedure described elsewhere *(Alyami M et al., Eur J Surg Oncol. 2017)*. Blood and peritoneal liquid samples where conditioned in ice and immediately centrifuged, separated in total and ultrafiltered (Uf) fractions, then frozen until analysis using a validated method based on flameless atomic absorption spectrophotometry. Frozen peritoneal biopsies were kept at −20°C until analysis with laser-induced breakdown spectroscopy.

Results

39 PIPAC were performed in our institution since July 2016. Primary analysis was performed on two female patients. Patient 1 aged 74 had a history of recurrent ovarian cancer with nonresectable carcinomatosis (PCI 18), (4th PIPAC with oxaliplatin). Patient 2 aged 69 had a history of gastrectomy for gastric cancer with metachronous carcinomatosis (PCI 11), (1st PIPAC with doxorubicin-cisplatin).

Patient	T	Conc. Blood (ug/l)	Conc. Peritoneal (ug/l)
1	T0	6	7
	T15	212	366,286
	T30	201	333,909
	T45	233	284,294
	T60	262	–
	T120	179	–

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	T240	137	–
Patient 2	T0	<LOQ	<LOQ
	T15	26	10,990
	T30	152	15,034
	T60	131	8221

Conclusion

On both patients PIPAC shows, compared to HIPEC, highest peritoneal level of platinum salt and about a 10 fold lowest blood level of platinum salt. Tissue penetration is on ongoing analysis. Those encouraging preliminary results shows the good ratio efficacy/toxicity of PIPAC procedures and have to be confirmed on more patients and by tissue analysis.

F10
FEASIBILITY, SAFETY AND EFFICACY OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) FOR PERITONEAL METASTASIS: A REGISTRY STUDY

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Objectives

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is a novel drug delivery system with superior pharmacological properties for treating peritoneal metastasis (PM). Safety and efficacy results of PIPAC with cisplatin/doxorubicin or oxaliplatin from a registry cohort are presented.

Methods

IRB-approved registry study (NCT03210298). No predefined inclusion criteria, individual therapeutic recommendation by the interdisciplinary tumor board. Safety assessment with CTCAE 4.0. Histological assessment of tumor response by an independent pathologist using the 4-tied Peritoneal Regression Grading System (PRGS). Mean PRGS and ascites volume were assessed at each PIPAC.

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Results

A total of 142 PIPAC procedures were scheduled in 71 consecutive patíents with PM from gastric (n = 26), colorectal (n = 17), hepatobiliary/pancreatic (n = 9), ovarian (n = 6), appendiceal (n = 5) origin; Pseudomyxoma Peritonei (n = 4) and other tumors (n = 3). Mean age was 58 ± 13 years. Patients were heavily pretreated. Mean PCI was 19 ± 13. Laparoscopic non-access rate was 11/142 procedures (7.7%). Mean number of PIPAC/patient was 2. All patients were eligible for safety analysis. There was no procedure-related mortality. There were 2.8% intraoperative and 4.9% postoperative complications. 39 patients underwent more than one PIPAC and were eligible for efficacy analysis and PRGS could be assessed in 36 of them. In 24 patients (67%), PRGS improved or remained unchanged at PIPAC#2, reflecting tumor regression or stable disease. Ascites was present in 24 patients and diminished significantly under therapy. Median survival was 11.8 months (95% CI: 7.45–16.2 months) from PIPAC#1.

Conclusion

PIPAC is feasible, safe and well-tolerated, and can induce histological regression in a significant proportion of pretreated PM patients.

F11
PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) FOR PERITONEAL METASTASES IN SOLID ORGAN GRAFT RECIPIENTS: FIRST EXPERIENCE

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Objectives

Therapy of peritoneal metastases (PM) in solid organ transplant recipients is challenging. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) might constitute a new therapeutic opportunity for these patients.

Methods

Single-center, retrospective analysis of prospective registry data (NCT03210298) in a tertiary care center between 1.7.2016 and 31.12.2017. Intraperitoneal administration of oxaliplatin 92 mg/m2 body surface or of a combination of cisplatin 7.5 mg/m2 and doxorubicin 1.5 mg/m2, repeated every 6 weeks. Objective tumor response was documented via histology (Peritoneal Regression Grading Score, PRGS), adverse events according to CTCAE 4.0.

Results

Out of 71 consecutive patients treated with PIPAC, two (2.8%) were solid organ transplant recipients. The first patient had metachronous PM of colonic origin after liver transplantation. The second patient had synchronous PM of pancreatic origin after combined kidney-/pancreas transplantation. After repeated combined systemic and PIPAC chemotherapy, objective histological response was documented in both patients. No adverse events > CTCAE 2 were recorded. There was no measurable liver or renal toxicity. PIPAC procedures could be repeated (2, resp. 3 cycles) without interruption of immunosuppressive medication or impairment of plasmatic drug level. The first patient passed away 7 months after first PIPAC, the second patient is still alive after 8 months.

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Conclusion

PIPAC can induce objective regression of PM in solid organ transplant receivers. PIPAC does not induce measurable organ toxicity and does not interfere with immunosuppressive therapy.

F12
PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY WITH LOW-DOSE CISPLATIN AND DOXORUBICIN (PIPAC C/D) IN PATIENTS WITH GASTRIC CANCER AND PERITONEAL METASTASIS: A PHASE-II TRIAL (PIPAC-GA1)

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Objectives

Efficacy of 2nd and 3rd line chemotherapy in recurrent gastric cancer with peritoneal metastasis (RGCPM) is limited. We assessed the feasibility, safety and activity of intraperitoneal chemotherapy as PIPAC C/D in RGCPM after ≥1 line of intravenous chemotherapy.

Methods

Open-label, single-arm, Phase II ICH-GCP Clinical Trial (NCT01854255) Patients were scheduled for 3 courses q42 days of low-dose PIPAC with doxorubicin 1.5 mg/m2 and cisplatin 7.5 mg/m2. Primary endpoint was objective tumor response (RECIST 1.1). Secondary endpoints were safety (CTCAE 4.0), histological tumor regression (PRGS) and overall survival.

Results

25 patients were enrolled. They were heavily pretreated (gastrectomy: 60%, 2nd-line situation: 64%, 3rd line: 20%, ≥4th line: 16%). 10/25 (40%, ITT) patients had an OTR. Complete or major regression on histology was observed in 9/12 (75%) patients who underwent at least 2 PIPAC cycles. Mean overall survival was 8.4 months (13.1 months in patients with PCI < 12). There were no treatment-related deaths, no grade 4 toxicity and four (16%) grade 3 toxicities.

Conclusion

PIPAC C/D is well tolerated and active in patients with RGCPM. Survival is encouraging. Randomized controlled trials should now be designed.

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F13
QUALITY OF LIFE OF PATIENTS WITH PERITONEAL METASTASIS OF GASTRIC ORIGIN (PMGC) TREATED WITH PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY WITH LOW-DOSE CISPLATIN AND DOXORUBICIN (PIPAC C/D) IN THE SALVAGE SITUATION: RESULTS FROM A PHASE-II TRIAL

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Objectives

PMGC have a poor prognosis and therapeutic options are limited. Intraperitoneal chemotherapy (IPC) has a dose-dependent local toxicity limiting its application in spite of documented efficacy in PMGC.

Methods

Open-label, single-arm, Phase II Trial (NCT01854255). Intervention: 3 courses q42 days of low-dose PIPAC with doxorubicin 1.5 mg/m2 and cisplatin 7.5 mg/m2 as stand-alone treatment. QoL, a secondary endpoint, was assessed longitudinally before each PIPAC cycle by QLQ-30 questionnaire of EORTC.

Results

25 patients (M:F = 10:15, mean age 55 ± 13 years) were enrolled. They were heavily pretreated (gastrectomy: 60%, 2nd-line situation: 64%, 3rd line: 20%, ≥4th line: 16%). At baseline, global QoL was 55 ± 26% and depended on the number of previous chemotherapy lines ($p = 0.06$). Prominent complaints were insomnia (30 ± 30%), fatigue (29 ± 20%) and abdominal pain (29 ± 33%). 43 PIPAC were performed (1 PIPAC, n = 25; 2 PIPAC, n = 12; 3 PIPAC, n = 6). QoL did not deteriorate significantly under PIPAC therapy ($p = 0.52$). Abdominal pain increased significantly ($p = 0.03$). Gastrointestinal symptoms such as diarrhea ($p = 0.17$), constipation ($p = 0.68$) and nausea ($p = 0.71$) were stable under PIPAC treatment.

Conclusion

PIPAC C/D is relatively well tolerated in advanced, therapy-resistant PMGC.

F14
ELECTROSTATIC PRESSURIZD INTRAPERITONEAL AEROSOL CHEMOTHERAPY FOR UNRESECTABLE PERITONEAL CARCINOMATOSIS: EXPERIENCE OF 125 PROCEDURES

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Objectives

Unresectable peritoneal carcinomatosis treated with systemic chemotherapy has a poor prognosis. Adding EPIPAC can be valuable. This research assessed its safety and therapeutic outcomes after several procedures.

Methods

A retrospective analysis of prospectively collected data of patients treated with EPIPAC was done.

Results

One hundred twenty-five procedures have been performed in 47 patients. Most patients had a primary tumor of colorectal (N = 16), gastric (N = 10), ovarian (N = 3) or esophageal (N = 3) origin. Thirty-nine patients had a history of systemic chemotherapy and six patients underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. During EPIPAC, one patient had an iatrogenic small bowel perforation that was successfully sutured. Two patients developed a toxic inflammation of the abdominal wall that was treated conservatively. EPIPAC was usually performed in day clinic and in combination with systemic chemotherapy (N = 2). Restaging and analysis of peritoneal biopsies after 3 EPIPACS showed disease regression (N = 3), stable disease (N = 8) or progression (N = 11). Evaluation of treatment response after 6 EPIPACS revealed disease regression (N = 1), stable disease (N = 1) and progression (N = 2). After a mean follow-up of 8.2 months (0–28) since first EPIPAC, 27 patients have died. In those patients who underwent at least 3 EPIPACS and initially demonstrated stable disease or regression, five of 11 patients have died after a mean follow-up of 13.5 month (4–28).

Conclusion

EPIPAC is safe to treat unresectable peritoneal carcinomatosis. In those patients who underwent at least three procedures, disease response was observed in half of cases, demonstrating the value of EPIPAC in progressive peritoneal carcinomatosis. Combination with systemic treatment is certainly recommended.

F15

OXALIPLATIN USE IN PRESSURIZED INTRAPERITONEAL AEROSOLE CHEMOTHERAPY (PIPAC) IS SAFE AND WELL TOLERATED: A MULTICENTER STUDY

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Objectives

Pressurized intraperitoneal chemotherapy (PIPAC) is a relatively new drug delivery method used in patients with peritoneal metastases of primary or secondary origin. Oxaliplatin was reluctantly used in PIPAC due to feared toxicity, especially abdominal pain. The objective of this multi-institutional study is to assess oxaliplatin-associated tolerance profile on a large cohort of patients.

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Methods

251 oxaliplatin-based PIPAC (92 mg/m²) were performed in 100 patients in five European centers specialized in the treatment of peritoneal carcinomatosis. The treatment was repeated every 6 weeks at 37°C and 12 mmHg. The data were collected and analyzed retrospectively based on personal and clinical variables. The main outcome criterion was tolerance to treatment according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Results

The cohort consisted of 56 male and 44 female patients that were treated for unresectable PC of various origins: colorectal 66%, gastric 15%, ovarian 5%, mesothelioma 3%, pseudomyxoma 2%, other (biliary, pancreatic, endocrine) 9%. The mean PCI was 18.78 (±10.60). An average number of 2.5 PIPAC were performed per patient (range 1 to 8). Abdominal pain was present in 23% of patients (9% grade III; 2% grade II; 12% grade I). Out of the 9% grade III patients only 3% needed a change in the PIPAC drug. Hematologic and renal toxicity was grade II or lower in a limited number of patients. Surgical complications grade III and IV were accounted for in 4 patients (two hematomas, two surgical site infections) whereas one respiratory grade V toxicity was recorded in a patient with a preexistent respiratory condition. 48% subjects presented with symptom improvement.

Conclusion

Oxaliplatin based PIPAC is safe and efficient in the treatment of symptomatic PC of various origins. Severe abdominal pain is observed in a minority of cases. Further clinical trials are expected in order to evaluate oncologic efficacy.

F16

FASCINATING PIPAC – THE COMPLEX ANALYSIS OF CURRENT WAYS OF PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY DEVELOPMENT

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Objectives

To the one of the very ambitious clinical solutions targeted onto resolving many of the problems and challenges associated with specialized peritoneal carcinomatosis (PC) treatment belong in recent years the proposed by scientific team of Prof. Reymond an innovative pressurized intra peritoneal aerosol chemotherapy (PIPAC). The method involves the combination of laparoscopic mini – invasive surgical techniques with a modern way of delivering the drug in the form of appropriately dispersed drops of aerosol under pressure. In recent time we can observe new and very interesting concepts of development of this technique. The aim of our study was the perform a scientific analysis of currently proposed ideas and novel applications of PIPAC.

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Methods

In our study we have analyzed data published since 2011 according to the technical and theoretical aspects of PIPAC. Additionally we have supported our material with self-Department obtaind data from pre-clinical and clinical studies. During the literature search we have used the most popular open database collections including Pubmed, ProQuest and Google Scholar. To our study we have selected the material in which authors have presented new concepts and ideas important for this drug delivery method development.

Results

From the whole number (n = 67) of selected for analysis papers according to the PIPAC technique we found papers which were related only to the topic of new concepts; new ideas; new solutions; device descriptions; technique modifications; novel types of use and unusual use of this method. The found material were supported by our self-findings obtained in pre-clinical and clinical studies performed in our Department since 10.05.2017 when the first PIPAC procedure were performed in our center.

Conclusion

The PIPAC drug delivery method is a technique which is from year to year more and more described in the literature. As the number of publications increases, the number of new ideas and solutions that more and more influence onto the development of PC patients' treatment is also growing. Especially in last two years there has been presented some interesting solutions which could in the future play an important role in PIPAC development. Our self-obtained material shows that especially nanomedicine alike the use of device combinations could be very interesting in this fascinating PIPAC development.

F17

TARGET TISSUE EFFECT OF HYPERTHERMIC INTRACAVITARY NANOAEROSOL THERAPY (HINAT): AN EX-VIVO STUDY

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Objectives

Hyperthermic Intracavitary NanoAerosol Therapy (HINAT) has been proposed recently as a novel drug delivery technique for intraperitoneal chemotherapy. Claimed advantages of HINAT are a homogeneous drug repartition and a superior depth of tissue penetration.

Methods

Ex-vivo study in the inverted bovine bladder model. Outcome criteria: tissue concentration (doxorubicin: DOX and cisplatin: CIS) and depth of tissue penetration (DOX). The atomizer ATM220® was operated as described previously (Pabst et al., 2018). First experiment: DOX 3 mg in NaCl 0.9% 50 ml and CIS 15 mg in NaCl 0.9% 150 ml; 2 bladders, 3 × 3 biopsies at the top, in the middle and the bottom. Second experiment: DOX 100 mg in 50 ml (undiluted); 3 bladders, same biopsies. Blind measurement of DOX tissue penetration

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in triplicate by an independent pathologist by fluorescence microscopy (FM). CIS and DOX tissue concentrations measured by a GLP-certified laboratory. DOX loss was quantified by directing the leaking gas through saline solution.

Results

First experiment: Using usual PIPAC CIS/DOX concentrations, target tissue concentration was below detection margin for both. FM for DOX revealed unspecific tissue staining, without drug uptake in cell nuclei. Second experiment: Using undiluted DOX, median tissue concentration was 23.4 ± 21.5 ng/ml. Distribution of DOX within the bladder was homogeneous. No DOX was detected in the leaking gas.

Conclusion

ATM220® is not able to deliver CIS to the target tissue in this ex-vivo model. To match DOX tissue concentration reported after PIPAC C/D, a 33 times higher upstream DOX concentration is needed. DOX tissue concentration was homogeneous. As there is no uptake of DOX into the nuclei, biological effect of HINAT should be evaluated in survival animal studies before first in-human use. HINAT requires the handling of large doses of highly concentrated DOX, which induces a potential risk of significant occupational exposure.

F18

LAPAROSCOPIC SURGERY IN ADVANCED GASTRIC CANCER (T3-4A, N1-3B, M0) COMBINED WITH HIGH PRESSURE AEROSOL CHEMOTHERAPY FOR PERITONEAL CARCINOMATOSIS (PC) PROPHYLAXIS AND TREATMENT

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Objectives

Locoregional spread of gastric cancer in the main cause for failure after potentially radical surgery. Peritoneal spread in gastric cancer is generally observed in 40 to 50% of the patients. There is no established standard for treating gastric cancer with peritoneal spread. PIPAC) is a system that improves logoregional delivery of the chemotherapy agents using the laws of physics. This therapy is based on breaking up chemotherapy agents into particles of 10–15 microns and delivering them in a concentration of 10% of the systemic dose under pressure of 15 mmHg for 30 minutes. Prevention and therapy of PC is the main indication for PIPAC which have promising initial results.

Methods

In prospective 12 patients had laparoscopic gastrectomy (7 total and 5 subtotal) with D2 lymph node dissection and intracorporal anastomosis due to gastric cancer. After finishing the reconstructive stage we applied PIPAC for 30 minutes. This procedure was repeated after 30 days for a total of 3 times. We analyzed retrospectively 14 laparoscopic gastrectomies due to gastric cancer for a past period of 1 year (poorly differentiated, diffuse type) actively searching for PC.

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Results

In 8(57%) of the retrospective patients PC being actively searched for, was established at the end of the first year after surgery. Three of the patients in the aerosol group have reached the end of the first year with no data supporting PC, the others remain to be analyzed.

Conclusion

The introduction of laparoscopy in the surgical practice for the treatment of gastric cancer has led to better postoperative care, shortening of hospital stay and faster return to normal patient activity. Even this early in its studies it is safe to say that PIPAC has better pharmacological capabilities compared to HIPEC and systemic chemotherapy for the treatment of peritoneal carcinosis as in vitro, animal studies and clinical data support this statement.

F19

MULTICENTER COMPREHENSIVE METHODOLOGICAL AND TECHNICAL ANALYSIS OF 832 PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) INTERVENTIONS PERFORMED IN 349 PATIENTS FOR PERITONEAL CARCINOMATOSIS TREATMENT: AN INTERNATIONAL SURVEY STUDY.

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Objectives

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new drug delivery method offered in selected patients suffering from non-resectable peritoneal carcinomatosis (PC). As reported experience is still limited, we conducted a survey among active PIPAC centers aiming to report their technical approach and clinical findings.

Methods

An online survey was sent to active PIPAC centers worldwide. The questionnaire consisted of 34 closed questions and was conducted over a period of 3 months beginning in March 2017.

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Results

Nine out of 15 contacted centers completed the questionnaire totaling 832 PIPAC procedures in 349 patients. Most common indications for PIPAC were PC from gastric, ovarian and colorectal origin. The mean time between each PIPAC procedure was 6 to 8 weeks. Seven of nine (77.8%) centers evaluate the PCI at every PIPAC procedure. At least four tissue samples for histopathology analysis were retrieved in 5 (55.6%). All centers (100%) use the same chemotherapy protocol: oxaliplatin at a dosage of 92 mg/m2 for PC of colorectal origin and a combination of cisplatin and doxorubicin at a dosage of 7.5 mg/m2 and 1.5 mg/m2, respectively, for other types of PC. Eight centers (88.9%) perform routine radiological evaluation before first PIPAC and after third PIPAC.

Conclusion

These data confirm that PIPAC procedures are homogeneously performed in established centers. Standardization of the procedure will facilitate future international multicenter prospective clinical trials. This results has been published in EJSO - M.Nowacki et al. Eur J Surg Oncol. 2018 Feb 22. pii: S0748-7983(18)30674-7. doi: 10.1016/j.ejso.2018.02.014.

F20

FIRST CASES OF MONOPORTAL PRESSURIZED INTRAPERITONEAL AEROSSOL CHEMOTHERAPY (PIPAC) IN BRAZIL.

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Objectives

The first cases of PIPAC with locally developed monoportal device in Brazil were treated between December 2017 and April 2018 by the Peritoneal Diseases Study Group at Santa Rita Hospital - Santa Casa de Porto Alegre.

Methods

The first nine procedures of PIPAC performed in our group and the surgical aspects and clinical characteristics of the patients are described.

Results

Five females patients were treated with this technique within a four months time span. A total number of nine procedures were performed. Our cases were managed in a multidisciplinary setting. PIPAC was performed with a monoportal device designed and previously tested in animal models. The Brazilian regulatory health agency subsequently granted approval for human use in November 2017. One gastric cancer, two ovarians cancer and two pancreatic cancer cases were included. At the time of the first PIPAC procedure, median patient age was 62,2 (51–73) years. Patients were treated with a planned six-week interval between procedures. The maximum number of PIPAC procedures performed in the same patient was three (in one patient with gastric cancer and one with ovarian cancer). The PIPAC drug protocol utilized was cisplatin 7,5mg/m^2 plus doxorrubicin 1,5 mg/m^2. Four patients received systemic treatment (ST) associated with

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PIPAC protocol. The local and ST were alternated in a multidisciplinary discussed schedule, which considered dose intensity, risk of complications (such as bleeding or neutropenia) and performance status (PS). The ST included trastuzumab for gastric cancer (n = 1), paclitaxel for ovarian cancer (n = 1), gemcitabine for ovarian cancer (n = 1) and FOLFIRINOX for pancreatic cancer (n = 1). One patient with pancreatic cancer was treated with no associated ST due to PS limitation. Median hospital stay after PIPAC was 5 days (1–13).

Conclusion

PIPAC performed with a monoportal device was feasible in the population described. These findings are compatible with the data previously described by our group. The scheduling routine including PIPAC and associated ST seems to benefit from a multidisciplinary approach and this can play a critical role in minimizing potential toxicity.

F21

COMPLICATIONS, ADVERSE EVENTS AND INFLAMATORY RESPONSE MARKERS IN A BRAZILIAN CASE SERIES OF PATIENTS TREATED WITH PRESSURIZED INTRAPERITONEAL AEROSSOL CHEMOTHERAPY (PIPAC)

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Objectives

PIPAC intraperitoneal drug delivery characteristics may improve the overall toxicity profile commonly observed in patients treating advanced peritoneal carcinomatosis. Few studies have systematically addressed this issue, particularly in describing objective parameters as inflammatory response markers.

Methods

To describe the complications, adverse events (AE) and inflammatory response markers (IRM) in the first monoportal PIPAC procedures performed in Brazil. Patients who underwent PIPAC had blood samples collected before and after procedures. Biochemical parameters evaluated included c-reactive protein (CRP), leukocyte count (Lc), albumin (Alb), creatinine (Cr) and liver enzymes.

Results

Nine procedures were performed in five patients between December/2017 and April/2018. Four patients received systemic treatment (ST) alternating with PIPAC. The most common postoperative grade II/III AE (according to CTCAE-4) were nausea (44,4%) and abdominal pain (55,5%). High intensity pain was observed in three patients, leading to further radiological imaging in one case and video laparoscopy in two others. Investigation revealed mild peritoneal inflammatory findings in two cases and wound dehiscence in one patient. One patient with pancreatic cancer and performance status (PS) 2 who was not receiving ST died 25 days after PIPAC due to disease progression. All patients had an increase in CRP levels measured

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24 hours after surgery. The mean CRP increase was 50.3 mg/L. Cr levels were not changed at the first postoperative day. Liver parameters were at normal range before following procedures. Two patients had an expressive decrease (³1.0 g/dL) in Alb (one after first and other after third procedure). Two patients had concomitant relevant increase of Lc (>12 G/L) and CRP.

Conclusion

Abdominal pain and nausea were the most common postoperative AE, associated with a transitory inflammatory response. These clinical findings could be explained as a consequence of drug-induced chemical peritonitis after intraperitoneal vaporization, yet mentioned before in literature. In our initial experience, there was no relevant systemic toxicity after PIPAC and the alternation with ST seems feasible and well tolerated. Mortality was related with disease progression in a patient with pancreatic cancer and PS, which should alert for avoid indicating this procedure to patients with deteriorating general condition.

F22

PIPAC, AS AN ALTERNATIVE FOR THE TREATMENT OF UNRESECTABLE PERITONEAL CARCINOMATOSIS. EXPERIENCE OF A FRENCH CENTER.

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Objectives

PIPAC is proposed as a novel treatment used for the symptomatic management of peritoneal carcinomatosis, in patients at high surgical risk or even with the aim of reversing the evolution of the disease.The objective of this work is to analyze the results obtained by our center, in terms of morbi-mortality and efficacy.

Methods

All patients were included between July 2016 and February 2018 with peritoneal, synchronous or metachronous carcinomatosis. Peritoneal carcinomatosis was characterized quantitatively according to the rate of peritoneal carcinomatosis during each procedure. Complications were analyzed according to the CTCAE classification.

Results

22 patients were included, 43 PIPACs were performed. According to the etiology, 8 had gastric origin, 6 gynecological and 6 colo-rectal. In 12 cases, at least 2 procedures were performed, stabilizing the initial PCI in 6 or decreasing in 5. Ten patients with CTCAE 2 and 3 complications were found. The most frequent were postoperative pain, followed by nausea and vomiting No case of mortality was found. The average hospital stay was 2.8 days.

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PCI response after the second procedure			
Patient	Initial PCI	Final PCI	Response
1	21	16	decline
2	12	6	decline
3	30	30	stable
4	6	6	stable
5	9	7	decline
6	32	34	increase
7	15	8	decline
8	18	8	decline
9	23	23	stable
10	15	15	stable
11	19	19	stable
12	19	19	stable

Conclusion

PIPAC is a procedure with an acceptable risk. Stabilization of the PCI can be achieved in more than 50% of cases. More studies are needed to analyze its long-term effectiveness.

Key words: peritoneal carcinomatosis-ovary-stomach-colorectal-cytoreduction and intra-abdominal chemotherapy.

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F23
PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) BEFORE CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR NONRESECTABLE PERITONEAL METASTASIS

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Objectives

PIPAC is a recent approach for intraperitoneal chemotherapy with promising results for patients with nonresectable peritoneal metastasis (PM). The aim of this study was to describe the clinical characteristics and extent of disease of the patients who became resectable after PIPAC and undergone cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods

This is a retrospective analysis of prospective maintained PIPAC database of Lyon Sud university hospital. All patients diagnosed with non-resectable PM who became resectable after PIPAC were included. Outcome criteria were adverse events during PIPAC cycles according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0., Secondary CRS and HIPEC.

Results

Four hundred thirty seven PIPAC were applied in 146 consecutive patients between December 2015 and March 2018: among them 26 patients (17.8 %) underwent 76 PIPAC and were scheduled for secondary CRS and HIPEC. PM was from colorectal, gastric, ovarian, malignant mesothelioma, or other origins in 2, 13, 7, 3 and 1 patients, respectively. Nineteen (73%) female. At the time of the first PIPAC, median age was 58.6 years (32–76.3). Median PCI was 14.5 (1–39). Seven (27%) patients underwent more than 2 lines of preoperative chemotherapy. All patients had systemic chemotherapy alternating with PIPAC. Median consecutive PIPAC cycles were 3 (1–8). Overall complications occurred for 3 PIPAC (4%) and there was no major complication (CTCAE - III, IV). Finally, Secondary complete CRS and HIPEC were achieved in 21 patients (14.4%) and for 5 patients CRS were not possible. Among Patients who underwent CRS and HIPEC 15 patients (76.2%) alive without recurrence, 2 patients (9.5%) alive with recurrence and 3 patients (14.3%) died.

Conclusion

Complete CRS and HIPEC can be achieved in selected patient with non-resectable PM after repeated PIPAC. Further prospective study is needed to evaluate this indication.

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F24
RENAL TOXICITY AFTER REPEATED PRESSURIZED INTRAPERITONEAL AEROSOL CHEMOTHERAPY (PIPAC) OF UNRESECTABLE PERITONEAL METASTASIS

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Objectives

PIPAC is a recent approach for intraperitoneal chemotherapy with promising results for patients with peritoneal metastasis (PM). We aimed to report data on renal toxicity for patients who received repeated PIPAC with at least 3 cycles.

Methods

All patients who underwent at least 3 PIPAC cycles of cisplatin (7.5 mg/m2) and doxorubicin (1.5 mg/m2) for non-resectable PM were analyzed regarding postoperative renal toxicity.

Results

Among 103 patients registered in our database between December 2015 and September 2017, 43 patients underwent at least 3 PIPAC cycles with a total of 175 PIPAC. Median age was 59.8 years, 24 (55.8%) female patient and median BMI was 22.2. The most common origin of PM was gastric 22 (51.1%) and ovarian 11 (25.6%) patients. Median PCI was 17 (5–39). For 39 (90.1%) patients, systemic chemotherapy was performed with PIPAC. Forty-three (100%), 17 (39.5%), 14 (32.5%), 8 (18.6%), 3 (7%), 2 (4.7%) and 2 (4.7%) patients underwent a third, fourth, fifth, sixth seventh, eighth and ninth PIPAC, respectively. Repeated PIPAC did not induce significant acute nor cumulative renal toxicity in all patients.

Conclusion

Repeated PIPAC did not induce clinically relevant renal toxicity. Renal function remained stable even after 9 PIPAC cycles in some patient.

F25
DOES PIPAC C/D POTENTIATE SYSTEMIC PD-1 IMMUNOTHERAPY FOR CONTROLLING PERITONEAL METASTASIS? REPORT OF A LONG-LASTING COMPLETE REMISSION IN THE SALVAGE SITUATION

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Objectives

Yolk sac tumors (YST) are rare malignant endodermal primitive tumours mostly originating in the gonads and metastasize to the peritoneum in 1/3 patients. Standard therapy is cytoreductive surgery combined with platin-based therapy. Outcome of patients with platinum refractory YST who relapse after stem-cell transplantation is dismal. No significant progress in therapy has been made within the last years.

Methods

We report the case of a 39-year-old female patient with a history of extragonadal YST diagnosed in 07/2015. The patient had 3 open surgeries for cytoreduction and received 5 lines of palliative systemic chemotherapy (1) cisplatin, etoposide and bleomycin; 2) paclitaxel, ifosphamide and cisplatin; 3) gemcitabine, oxaliplatin and paclitaxel; 4) etoposide and thiotepa) 5) 3 autologous stem cell transplantations after high-dose chemotherapy with carboplatin and etoposide. In 04/2017, immunotherapy with anti-PD1 antibody was started. Staging after 5 cycles nivolumab showed intraabdominal POD but no extraperitoneal disease.

Results

The patient received 1st PIPAC with low-dose cisplatin and doxorubicin (PIPAC C/D) in 07/2017. General condition was reduced (KI 70%). PCI was >25 with 1.6 L hemorrhagic ascites. The postoperative course was uneventful. Nivolumab therapy was continued. 6 weeks later, the 2nd cycle of PIPAC C/D was performed and a complete radiological (MRI), macroscopic (staging laparoscopy), histological (multiple peritoneal biopsies, no tumor cells (PRGS 1)) and cytological (no tumor cells) tumor response was documented. General condition and quality of life were largely restored. Due to severe hepatotoxicity, immunotherapy was then interrupted and the patient received high-dose corticoids. She received 3 further cycles of PIPAC C/D in 10/2017, 12/2017 and 03/2018 and is currently in long-lasting complete remission.

Conclusion

To our knowledge a combination of immunotherapy with PIPAC C/D was used for the first time in a patient with metastatic YST. This regimen induced a spectacular complete remission of the disease in the salvage, therapy-resistant situation, which has been sustained now for at least 10 months. This exceptional response might be explained by a locoregional immunomodulatory stimulation (by PIPAC C/D) of the peritoneal environment to systemic PD-1 antibody therapy. This hypothesis opens new research avenues in therapy of PM.

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ASSESSMENT OF THE AEROSOL DISTRIBUTION PATTERN OF A SINGLE-PORT DEVICE FOR INTRAPERITONEAL ADMINISTRATION OF THERAPEUTIC SUBSTANCES

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Objectives

To analyze the spatial distribution pattern of a therapeutic solution aerosolized into the peritoneal space using a single-port device.

Pleura and Peritoneum 2018; 1, Special Suppl, pp sA6–sA463, September 2018 • Copyright © 2018 Walter de Gruyter GmbH, Berlin / Boston

Methods

Analysis of the rate of intra-abdominal staining with aerosolized 2% silver nitrate in 5 porcine models.

Results

Assessment of differences in stain impregnation between the upper, middle, and lower abdomen did not reveal significant differences ($p = 0.42$). The median sum scores were 1 for the upper abdomen and 3 for the middle and lower abdomen.

Conclusion

Aerosolization does not reach all regions of the abdomen homogeneously. However, adequate exposure of the upper abdomen, mid-abdomen, and lower abdomen to chemotherapeutic agents can be achieved with PIPAC.

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DEVELOPMENT OF AN ORIGINAL EX-VIVO MODEL ALLOWING REAL-TIME PHARMACOKINETICS MEASUREMENTS DURING DRUG DELIVERY AS PRESSURIZED AEROSOLS: THE CAPNOCUP® MODEL

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Objectives

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is a generic drug delivery system. Physicochemical parameters of the aerosol, including e.g. pressure, temperature, electrostatic loading, droplet size, substance, formulations, etc. have to be optimized for each specific application. This requires validated preclinical models. We present an original ex-vivo model allowing real-time pharmacokinetics measurements during drug delivery as pressurized aerosols: the CapnoCup® model.

Methods

Further development of the inverted bovine bladder model (Schnelle et al., Pleura Peritoneum 2016). Anatomically, the bovine bladder lies intraperitoneally and is almost completely covered by serosa. In this ex-vivo model, the serosa is covering the inner side of the inverted bladder, forming after insufflation with CO2 a closed experimental volume of 3–5 L comparable to an human abdomen. Further development was needed to allow repeated pharmacokinetics measurements over time without need for exchanging the organ for each measurement at each timepoint of interest.

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Results

The bladder is hanging to a scale. The bottom of the inverted bladder is connected over a tube with a 2nd recipient (communicating vessels principle). The bladder and the 2nd recipient are filled with CO_2 at the same pressure (12–15 mmHg). The second recipient is placed on a second balance. The aerosol is then generated within the hanging bladder. It is possible to determine in real-time 1) the convective flux (liquid uptake into the bladder wall) by measuring $\delta W_{(bladder)}$, 2) the dripping of the solution along the serosa (the time of contact of the polymeric solution with the bladder wall) by measuring $\delta W_{(2nd\ recipient)}$ and finally to calculate the weight of the floating aerosol over time by a simple subtraction $Weight_{(floating\ aerosol)} = weight_{(volume\ aerosolized)} - \delta W_{(bladder)} - \delta W_{(2nd\ recipient)}$. By integrating the Area Under the Curve (AUC) it is possible to modelize drug uptake and dripping behaviour over time.

Conclusion

The CapnoCup® is a simple, reproducible and cost-effective ex-vivo model for optimizing intraperitoneal drug delivery as pressurized aerosols. The model permits assessment of pharmacokinetics parameters in real-time. It is not adequate for biological studies. The CapnoCup® model is expected to save hundreds or thousands of animal lives to optimize the physicochemical parameters and drug formulation for PIPAC.