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PIPAC EstoK 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: a randomized and multicenter phase II study

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Abstract

Background: Peritoneal metastasis (PM) from gastric cancer often remains undiagnosed until it reaches an advanced stage. Despite curative management combining perioperative systemic chemotherapy, cytoreductive surgery (CRS), and hyperthermic intraperitoneal chemotherapy (HIPEC), treated patients' 5 year survival rate remains under 20 % when patients are carefully selected. Palliative intravenous chemotherapy in patients with non-resectable cancer is frequently associated with poor long-term benefit and an estimated survival time below 1 year. Recently, two retrospectives studies reported that Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) improves patients' overall survival without impairing their quality of life (QoL). This promising result needs however to be studied on large randomized clinical trial to validate the effect of PIPAC on survival and QoL of patients with gastric PM.

Methods: PIPAC EstoK 01 is a prospective, open, randomized multicenter phase II clinical study with two arms that aims at evaluating the effects of PIPAC with doxorubicin and cisplatin on patients with PM of gastric cancer with peritoneal cancer index (PCI) > 8, treated with systemic chemotherapy between two PIPAC procedures. Patients were randomized at the end of explorative laparoscopy and after signing a written consent. Patients received in the first experimental arm a treatment associating PIPAC and systemic chemotherapy (1 PIPAC then 2 IV Chemo) and systemic chemotherapy only in the control arm. Primary endpoint was progression-free survival from the date of surgery to the date of death, or to the end of the 5 year follow-up. Secondary endpoint was 2 year overall survival, morbidity, QoL and secondary resectability rate. The number of patients randomized was calculated to be 94.

Trial registration: Retrospectively registered.

Keywords: gastric adenocarcinoma, peritoneal carcinomatosis, Pressurized IntraPeritoneal Aerosol Chemotherapy, doxorubicin, cisplatin.

Introduction

Current management of peritoneal metastasis of gastric cancer

Peritoneal metastasis (PM) is a common phenomenon in advanced gastric cancer and leads to a terminal condition in a very short time. Despite recent progress regarding systemic chemotherapy using multi-drugs associations, median survival time is limited to 6 months with altered Quality of Life (QoL) after 4 months for all patients [1]. To date, the only hope of prolonged survival is associated with either a rare cancer mutation on a specific gene that expresses HER2 (Human Epidermal growth factor Receptor 2) [2] or the possibility to have a complete cytoreductive surgery (CRS) combined with intraperitoneal chemotherapy. However, CRS and HIPEC (hyperthermic intraperitoneal chemotherapy) are not always suited for this type of tumor and are only beneficial for patients who present limited peritoneal carcinomatosis (peritoneal cancer index PCI ≤ 8) [3, 4]. Taken together, these elements urge for a new therapeutic approach and strategy to develop treatments that fit better the conditions and outcomes of advanced gastric cancer with peritoneal carcinomatosis.

An innovative strategy: PIPAC

Carcinomatosis is known to have limited chemosensitivity because of poor drugs tissue penetration. Numerous preclinical and pharmacokinetic studies

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have demonstrated that the administration chemotherapy directly into the peritoneal cavity results in a several-fold increase in drug concentration within abdominal cavity compared with intravenous treatment. Similarly, a new innovative technology for intraperitoneal chemotherapy delivery, Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) was shown to significantly improve the conditions of administration and patient's outcome and survival with preserved QoL. This technique consists in delivering cytotoxic drugs by a pressurized aerosol directly into the abdominal cavity [5]. PIPAC is applied through laparoscopic access and a normothermic capnoperitoneum is established with a pressure of 12 mmHg. A cytotoxic solution is nebulized with a micropump into the abdominal cavity for 30 min. This treatment has been used for PM of various origins, with encouraging results in gastric cancer with median survival from 13 to 15 month [6–8].

Applying an aerosol in the peritoneal cavity allows for a homogeneous distribution of the chemotherapeutic agent within the abdomen. In addition, an artificial pressure gradient is generated to overcome tumor interstitial fluid pressures, which can often represent an obstacle in cancer therapy. The use of PIPAC results in higher local drugs concentration compared with conventional intraperitoneal or intravenous chemotherapy [9]. At the same time, the plasma concentration of the chemotherapeutic agent remains low, reducing potential side effects and organ toxicity. Recent experimental studies strengthen these findings and show that the main advantage of aerosol chemotherapy delivery in a close compartment reside in the high local drug penetration rate that counteracts the high pressure of the interstitial PM which reduces significantly secondary effect of systemic passage in patient [10]. Interestingly, PIPAC procedure was designed for repeated applications every 4–6 weeks. This therapeutic strategy allows for improved IP drugs impregnation while maintaining IV chemotherapy. We hypothesize, as suggested by the German team who designed the PIPAC technique, that drugs concentration under PIPAC delivery can be five times lower than in hyperthermic intraperitoneal chemotherapy (HIPEC). In our study, a dose of cisplatin at 10.5 mg/m^2 body surface in 150 mL NaCl 0.9% was used, immediately followed by doxorubicin at 2.1 mg/m^2 in 50 mL NaCl 0.9% at 12 mmHg and 37 °C for 30 min, as suggested by Tempfer et al. [11].

Methods and design

Protocol overview

PIPAC EstoK 01 is a prospective, open, randomized multicenter phase II clinical study aimed at evaluating the effects of PIPAC with doxorubicin + cisplatin on patients with PM of gastric cancer (Figure 1 – Flow chart study). Patients will be randomly assigned in a 1:1 ratio to: Arm A: intravenous chemotherapy + PIPAC with doxorubicin + cisplatin vs. Arm B: intravenous chemotherapy without PIPAC.

Measures of outcomes and assessments

Primary outcome: Progression free survival (2 years) will be measured defined as time from randomization to any clinical (ascites, abdominal pain, weight loss > 10 % of total body weight) and/or morphological signs (systemic metastases, ascites, progression on RECIST criteria) of recurrence (local or systemic) or death.

Secondary outcomes:

- Evaluation of 24 month overall survival.
- Evaluation of the safety and tolerability of the PIPAC procedure.
- Evaluation of the specific QoL (EORTC QLQ-C30 and the gastric cancer module [QLQ-STO22]).
- Feasibility of three successive PIPAC procedures, regarding repeated peritoneal access.
- Secondary resectability rate.

Main inclusion criteria: Patients 18 < age ≤ 75 years old with performance status (WHO) ≤ 2 with histologically evidenced synchronous or metachronous PM of a gastric adenocarcinoma cancer, including ADCI (adenocarcinoma with independent cells) or linitis, with PCI > 8. Patients with or without primary gastric tumor are eligible. Patients who received prior chemotherapy could be included at any time of the treatment. Patients affected by ovarian metastasis could be included in case of first surgical resection if mandatory or without surgical resection.

Main exclusion criteria: The following criteria exclude patients: distant metastases (liver, lung., etc.), patients presenting with an adenocarcinoma of the cardia Siewert I or II, patients with clinically significant ascites (> 3000 cc), pleural effusion requiring evacuation for respiratory failure, small bowel occlusion with no possible food intake, HER2 +++ tumor, contraindication to any drug contained in the chemotherapy regimen, weight loss > 20 % of total body weight, having any form of previous intra-abdominal chemotherapy or antibody therapy, presence of comorbidities, notably serious chronic diseases or organ failure, pregnancy or breastfeeding. Cytoreduction surgery is not allowed during PIPAC procedure.

Randomization: Written informed consent will be signed during the medical visit before diagnostic laparoscopy. The randomization will be

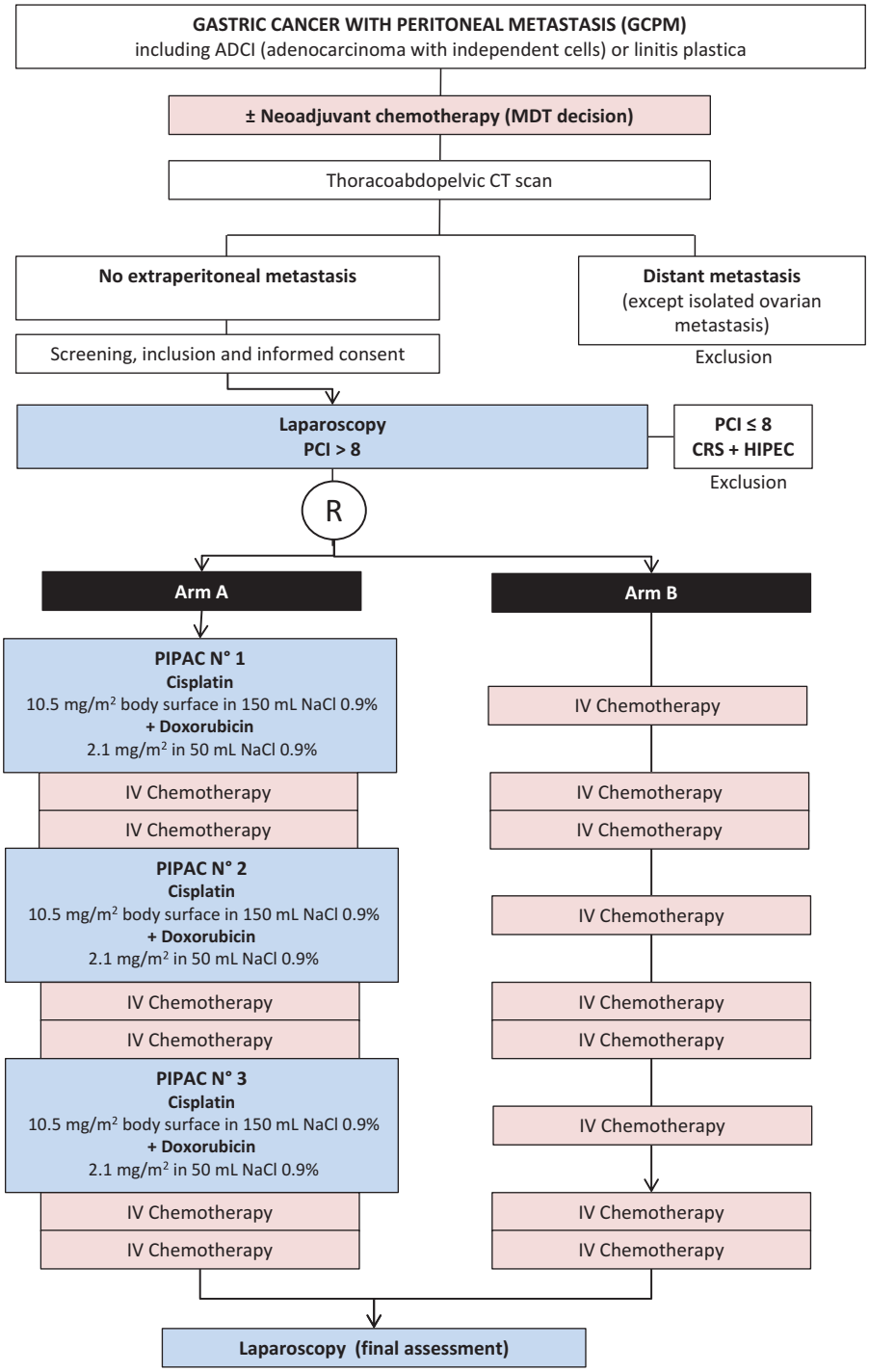

Figure 1: PIPAC EstoK 01 study flow-chart.

performed during the surgical procedure after verification of the inclusion and exclusion criteria. Once the inclusion and exclusion criteria are validated, each patient will be randomized using RandoWeb, an online randomization system (randoweb.aphp.fr). The randomization list will be generated by permutation blocks in a 1:1 ratio and will be stratified on the type of center. It will be generated by computer at the Saint-Louis Clinical Research Unit and the list will be sent in clear text to the sponsor. The allocation of patients to different groups of the study will involve the use of a secure, independent computer to ensure that the investigator cannot influence the results of this procedure. Randomization will be stratified by center and by type of previous chemotherapy in a 1:1 PIPAC: no PIPAC ratio.

Treatments

Pre-therapeutic work-up: Patients eligible for the study will be seen in clinics to check the inclusion and exclusion criteria. The patient will be required to give written informed consent to participate to this clinical study before any nonroutine screening tests or evaluations are conducted. The following assessments should be performed: performance status evaluation, upper intestinal endoscopy, endoscopic ultrasound (optional), thoraco-abdomino-pelvic CT scan, MRI (optional), laboratory exams: serum CEA, CA19.9; hemoglobin, leukocytes, neutrophils, platelets, glycemia, AST, ALT, LDH, total bilirubin, alkaline phosphatase, serum albumin, total protein, plasmatic APTT, PT and INR; creatinine clearance and serum creatinine, QoL assessment (QLQ-C30 and QLQ-STO 22).

Intravenous chemotherapy: In advanced gastric cancer, chemotherapy is the standard palliative treatment in patients with an acceptable clinical status because it provides better survival and QoL than supportive care. Combination of epirubicin, cisplatin, and fluorouracil (ECF) is a standard procedure widely used today. In the past decade, more drugs, including oral fluorouracil, docetaxel, oxaliplatin, and irinotecan, have proved to be effective for this indication. New first-line regimens demonstrated equivalence (epirubicin, cisplatin, and capecitabine [ECX]; epirubicin, oxaliplatin, and capecitabine [EOX]; and mFOLFOX) or superiority (docetaxel, cisplatin, and fluorouracil [DCF]) to CF or ECF [12–14]. FOLFIRI has been recently compared to ECX with a better time-to treatment failure [1]. FLOT who is an association of fluorouracil, leucovorin, oxaliplatin, and docetaxel has shown interesting results in patients with limited metastatic disease [15] and is currently evaluated in a phase III randomized study 5-fluorouracil and oxaliplatin with or without docetaxel in first-line chemotherapy advanced gastric cancer (GASTFOX study [16], Long-term benefit remains poor with overall survival still less than 1 year (7–9 months in most studies).

Patients will receive standard poly chemotherapy proposed by the oncologist as EOX, ECX, FOLFIRI, FOLFOX, ECF, or FLOT, or any new standard validated during the study, until progression or toxicity. All patients can be included, even in case of more than one line of chemotherapy.

Surgical technique: Explorative laparoscopy: PCI is determined according to Sugarbaker, based on lesion size and distribution [3]. Using a pictorial of the abdomen, each location of a 13 point list (central abdominal wall, epigastrium, right lower abdominal wall, right upper abdominal wall, right flank, left lower abdominal wall, left upper abdominal wall, left flank, pelvis, upper jejunum, lower jejunum, upper ileum, lower ileum) received a peritoneal carcinomatosis grade ranging from 0 to 3, i. e. no visible carcinomatosis, isolated tumor nodules, multiple tumor nodules, and confluent lesions. The sum of all 13 grades was noted as PCI.

– In case of PCI ≤ 8:

Patient is not included in the study and will receive the possibility to have the standard treatment of resectable PM with cytoreductive surgery and HIPEC, if the PM could be resectable.

– In case of PCI > 8:

Patient will be per-operatively randomized into our two groups: Arm A:IV chemotherapy and PIPAC or Arm B: IV chemotherapy alone.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC): After insufflation of a 12 mmHg of capnoperitoneum at 37 °C, two balloons safety trocars (10 and 12 mm) are inserted into the abdominal wall. A biopsy is taken for pathologic confirmation of PC during the first procedure and all following procedures in order to ascertain tumor regression grade [17]. Ascites volume is documented and ascites is removed. Then, a nebulizer CAPNOPEN© (Reger Medizintechnik, GmbH, Villingendorf, Germany) is connected to an intravenous high-pressure injector and inserted into the abdomen. The tightness of the abdomen is documented via a zero-flow of CO_2. Safety house is used to entirely cover the abdomen. A continuous suction is performed under the house by a surgical smoke extractor providing a second level of security in case of leak during the vaporization. Injection parameters are set at a flow rate of 30 mL/min and a maximum upstream pressure of 200 psi in the high-pressure injector. The injection is remote-controlled to minimize personnel exposure. The safety protocol with checklist containing all safety aspects as described previously [18] was systematically double-checked before administration of cytostatics. After application of doxorubicin (2.1 mg/m^2 in 50 mL NaCl 0.9 %) and cisplatin (10.5 mg/m^2 body surface in 150 mL NaCl 0.9 %), the therapeutic capnoperitoneum is maintained for 30 min at a temperature of 37 °C. Then, the chemotherapy aerosol is exhausted over a closed surgical smoke extractor. Finally, trocars are retracted and laparoscopy ended. No drainage of the abdomen is applied. The PIPAC procedure is repeated three times every 6–8 weeks with a median rate of PIPAC of 2.5/ patient because of possibility of nonaccess of the abdomen because of adhesions [18].

Laparoscopy for final evaluation: Explorative laparoscopy is performed at 3 months e. g. 1 month after the third PIPAC application for the experimental group. PCI and ascites volume are documented and tumor biopsy is taken in order to ascertain tumor regression. Ascites volume is documented and ascites is removed. Importantly, decision to perform this last laparoscopy will be made in accordance to the referring physician, surgeon, or oncologist.

In case of PCI major decrease under eight, after the three PIPAC procedures or after intravenous chemotherapy, extended biopsy will be perform. The tumor response confirmed by pathological analysis is analyze regarding guidelines prior published for post PIPAC analysis [17]. If confirmed a proposition to perform a cytoreductive surgery, including an HIPEC is discussed with the patient and the oncologist's teams, regarding general status.

Follow-up

After PIPAC, patients will remain in the standard hospitalization unit for 2 days. They will be evaluated with clinical examination daily. For the first postoperative day, laboratory exams will be performed in order to assess hematological, renal and hepatic function. Locoregional toxicity and systemic toxicity will be evaluated according to the Common Terminology Criteria for Adverse Events (CTC-AE V4.0) from the National Cancer Institute.

Once an early postoperative follow-up 4 weeks after PIPAC, the visits of follow-up are based on the date of the surgery every 3 months for the first 2 years following surgical procedure and twice a year for the last 3 years. At each visit, the patient will undergo a clinical examination, an evaluation of the QoL (using the QLQ C30),

an assessment of tolerance (CTCAE V3), an assay for tumor biomarkers (ACE and Ca19-9) and a CT scan of the chest and abdomen. For all patients clinical follow-up with all events and endpoints will be collected and analyzed during 5 years from their inclusion (except for patients who died, who were lost of follow-up or who expressed their refusal).

Criteria for premature discontinuation of the patient's study participation

Patients can be withdrawn from the study under the following circumstances: death, initiation of alternate anti-tumor therapy, toxicity, noncompliance (including loss of patient to follow-up), and voluntary withdrawal. After initiation of alternate anti-tumor therapy, toxicity e. g. normally patients receive an end of treatment (EOT) and are excluded e. g. from per-protocol analysis (PP), but not from the study, they will receive further follow up examinations and could be evaluated in the intention to treat population (ITT).

Sample size calculation and statistical considerations

Considering a survival analysis using a two-sided log-rank test, we fixed our bilateral type I error at 5% and we aimed a power of 85%. We assumed a median progression free survival in the control arm of 6 months and an expected median progression free survival in the PIPAC arm of 12 months. Thus, we need to observe 78 events corresponding to a sample size of 94 patients to be enrolled (equally balanced in each arm).

Ethical considerations, information giving and written informed consent

For each recruited patient into the study, written informed consent is essential prior to inclusion into the study after extensive information about the intent of the study, the study regimen, potential associated risks and side effects as well as potential alternative therapies. The investigator will not undertake any diagnostic measures specifically required for the clinical trial until valid consent has been obtained. Validation by National Ethical Committee will be performed before a patient is included into the study.

Discussion

Gastric cancer as a model for proof of concept of PIPAC efficacy

Patients with gastric PM are affected with terminal conditions; urging the use of other therapeutics than intravenous poly-chemotherapy leading to short median survival. The new concept proposed with CRS and HIPEC showed great success. However, the invasiveness of the HIPEC procedure requires that young patients have limited disease and controlled oncologic behavior through systemic treatment. These situations however are uncommon and HIPEC surgery for gastric PM only offers an 18% of overall survival at 3 years [19]. This is the worst survival rate in HIPEC procedures for a PM compared with other carcinomatosis diseases originating from colon, appendicular, or ovaries. For these reasons, we decided to first test PIPAC in this pathological type of carcinomatosis. In case of success, we offer to the medical community a scientific demonstration that PIPAC can help control PM with a limited toxicity, as previously reported.

In respect of Quality of Life

QoL has an important role in patients' survival with PM, especially in gastric cancer frequently associated with the worst survival. In these patients, continuous deterioration of their QoL is observed until death. Ethically, in palliative settings, improved survival can't be disconnected from an improvement of relative stability of quality of life. Two recent studies reported the impact of PIPAC procedures on QoL, without any deterioration, especially no additional gastrointestinal symptoms. We hypothesized that the respect of the QoL for a patient is as important as their survival in this particular peritoneal disease. For this reason, PIPAC represents one of the major solution to preserve the QoL in our preliminary experience.

Rescue CRS and HIPEC for unresectable peritoneal metastases down-staged by PIPAC

As CRS and HIPEC are the only curative treatments in PM, allowing a long-survival rate of 18% and even cure in 11% for PM of gastric cancer; PIPAC could be used as a neoadjuvant therapy with the CRS + HIPEC procedure. Several debates among the cancer community are currently being discussed to evaluate the future therapeutic potential of IV chemotherapy to down-stage PM of gastric origin, convert the cancer to a resectable stage and perform CRS + HIPEC. A number of small series were

published in this setting. Fava et al. reported the first three cases of bidirectional intraperitoneal and systemic chemotherapy with secondary CRS and HIPEC [20]. Similarly, Girshally et al. reported eight patients with diffuse PM that received CRS + HIPEC after neoadjuvant PIPAC procedures [21]. To explore the opportunity of rendering operable a non-operable PM, we believe that a randomized study offers robust and relevant information regarding non only PIPAC but also intravenous treatment.

Despite the fast spreading of the technique around the world, with more than a 1000 procedures performed in the primary German center, no randomized clinical study offering a robust scientific demonstration has been published. Reymond and colleagues publish a cohort of gastric PM treated with PIPAC alone allowing an improvement of median survival of 15.6 months [22]. The use of a new innovative health technology such as PIPAC to control PM is a major progress in cancer treatment, and its therapeutic benefits are not limited to gastric cancer but to all PM.

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Author contributions: CE is the study coordinator, obtained the grant and is responsible for the present paper. CE and MP have been involved in drafting the manuscript, in the study conception and design, assisted in writing the manuscript and have given final approval of the version to be published; IJ has been involved in the study conception and design. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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