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Randomized control trial comparing quality of life of patients with end-stage peritoneal metastasis treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC) and intravenous chemotherapy

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Abstract

Background: Peritoneal metastasis (PM) is a common occurrence in gynaecological and gastrointestinal cancers and is associated with poor survival. Patients typically present with ascites, abdominal pain, malnutrition, nausea, emesis, and bowel obstruction which significantly compromise the quality of life (QoL). The treatment remains a particular challenge, with palliative systemic chemotherapy being the standard of care. However, the efficacy of systemic chemotherapy is poor but with high potential for side effects and complications. QoL plays an important role in patients with PM and is deteriorating continuously until death. Thus, there is an obvious medical need for better therapeutic options in PM for prolonging survival and preserving QoL by reducing both disease-related symptoms and therapy side effects. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel technique for delivering pressurized normothermic chemotherapy into the abdominal cavity as an aerosol. This concept seems to enhance the effectiveness of intraperitoneal chemotherapy by taking advantage of the physical properties of gas and pressure by generating an artificial pressure gradient and enhancing tissue uptake and distributing drugs homogeneously within the closed and expanded peritoneal cavity.

Methods: The primary objective of this study is to assess QoL and symptoms in a consecutive cohort of patients with PM treated with PIPAC procedure in comparison with conventional systemic intravenous chemotherapy. QoL is assessed prospectively using European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (Version 3.0) questionnaire. QLQ-C30 is a 30-question self-administered questionnaire inquiring about global health status, 9 individual symptoms, and 5 functional scales. Baseline QoL is measured using the global physical health functional score, and symptom scores derived from EORTC QLQ30 questionnaire before starting therapy, followed by at 60, 120, and 180 days after the first intervention. Calculated sample size is 119 and rounded to 120. For each treatment group, sample size of 60 will be enrolled; Intervention model: IV chemotherapy group (control group) and PIPAC group (experimental group); Study type: prospective randomized control intervention trial

Discussion: All consecutive patients diagnosed with advanced end-stage PM are randomized to be treated with PIPAC or IV chemotherapy. The primary objective of this study is to determine the QoL after three cycles of PIPAC in comparison with six cycles of systemic chemotherapy. The secondary outcome measures include morbidity and mortality. Analysis is by intention to treat.

Results: The effect of systemic chemotherapy remains limited on the peritoneum due to poor vascularization and low penetration. Side effects after systemic chemotherapy for PM are relatively frequent. QoL plays an important role in these patients and is deteriorating continuously due to the disease or therapy related. Thus, there is need for better therapeutic options for prolonging survival and preserving QoL by reducing both disease-related symptoms and therapy side effects. PIPAC is a novel minimally invasive repeatable treatment modality which demonstrated potentially encouraging tumour response and only minimal toxicity in patients with PM of various origins. It can optimize local drug delivery and improve clinical outcome due to superior pharmacological properties as compared to systemic chemotherapy.

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Keywords: palliative chemotherapy, peritoneal metastasis, pressurized intraperitoneal aerosol chemotherapy (PIPAC), quality of life (QoL)

Introduction

Peritoneal carcinomatosis was regarded as a terminal disease with traditional palliative treatment options of systemic chemotherapy or palliative surgery having poor outcome [1]. The effect of systemic intravenous (IV) chemotherapy remains limited on the peritoneum due to low penetration and relative resistance of peritoneal nodules. Combining several agents has increased efficacy but is also associated with considerable risk for side effects with negative impact on quality of life (QoL) [2]. Hyperthermic intraperitoneal chemotherapy (HIPEC) overcomes some of the pharmacokinetic limitations and improves survival in selected patients [3, 4] at the price of high morbidity and a negative impact on QoL for several months after the procedure [5]

PM remains a particular challenge with sparse treatment options but high potential for side effects and complications. Patients with PM are frequently complicated by pain and gastrointestinal or urinary symptoms with a substantial impact on the QoL of these patients. The effect of systemic chemotherapy remains limited on the peritoneum due to low penetration and relative resistance of peritoneal nodules. Combining several active agents has increased efficacy but was also associated with considerable risk for side effects with negative impact on QoL. Thus, there is need for better therapeutic options in PM prolonging survival and improving QoL by reducing both disease-related symptoms and therapy side effects [6, 7].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel technique delivering normothermic chemotherapy into the abdominal cavity as an aerosol under pressure. Preliminary experiences reported in literature have documented the positive outcome of higher local bioavailability by applying pressure into the peritoneal cavity [8], by counterbalancing the elevated tumoural interstitial fluid pressure [9] and enhancing drug depth penetration with superior distribution. This prevents systemic side effects and organ toxicity typically seen with systemic chemotherapy like renal toxicity (cisplatin), neurotoxicity (oxaliplatin), and cardiac toxicity (doxorubicin) [10]. Feasibility, safety, and tolerance have been described in several studies already, and preliminary data on oncological efficacy are encouraging [11].

QoL is assessed in cancer patients using European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30(Version 3.0) questionnaire, a validated tool for assessing QoL [12]. The most widely used and generally accepted tool for assessing health-related QoL in oncology is the questionnaire launched by the EORTC. The core instrument has been validated in the general cancer population and consists of a global QoL scale, functional scales, and symptom scales. It includes 30 different items, split up into 6 scales, containing items for emotional (4 items), social (2 items) and physical functioning (5 items), cognitive (2 items) and role functioning (2 items), and further global health status (2 items). Better function is represented by higher mean scores in all scales. The questionnaire also provides symptom scores, including gastrointestinal items (nausea/vomiting, constipation, diarrhoea, and appetite loss) and pain. Lower scores indicate fewer symptoms. We choose a general questionnaire since different drugs were used and different cancers were pooled. There are only few studies which reported on QoL under PIPAC treatment so far, and there is an immediate need to evaluate role of PIPAC for these patients [13, 14].

Methods

This is a protocol of the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) Phase-3, monocentric, prospective randomized trial evaluating global physical health functional score according to EORTC-QLQ30 questionnaire in two groups of 60 patients each diagnosed with isolated PM: an experimental group treated with PIPAC alone and a control group treated with systemic palliative chemotherapy.

A longitudinal analysis will be performed for each individual patient for clinically significant (>10 points) changes in the global physical health functional scores and symptom scores derived from EORTC QLQ30 questionnaire. The study includes all consecutive patients diagnosed with isolated unresctable PM who met the inclusion and exclusion criteria.

Hypothesis of study

PIPAC is a safe, feasible, and tolerable treatment for patients with PM, with a potentially better QoL compared to systemic chemotherapy.

Trial population

Patients diagnosed with PM who met the inclusion and exclusion criteria.

Randomization

Randomization will be done before the initiation of the treatment. Stratified block randomization will be done. Stratification factors are tumour type and initial performance status.

Eligibility criteria

Key inclusion criteria:

1. Verified PM in colorectal cancer, ovarian cancer, gastric cancer, appendiceal cancer, or malignant mesothelioma
2. Age > 18 years
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
4. No indication for Cytoreductive Surgery (CRS) and HIPEC
5. Informed consent

Key exclusion criteria:

1. A history of allergic reaction to platinum-containing compounds or doxorubicin.
2. Ileus/obstruction
3. Extraperitoneal metastasis
4. Renal impairment, defined as Glomerular Filtration Rate (GFR) < 40 mL/min (Cockcroft–Gault equation)
5. Myocardial insufficiency, defined as New York Heart Association (NYHA) class > 2
6. Impaired liver function defined as bilirubin $\geq 1.5 \times$ UNL (upper normal limit)
7. Inadequate haematological function defined as Absolute neutrophil count (ANC) $\leq 1.5 \times 109$/L and platelets $\leq 100 \times 109$/L

Pertinent demographic and surgical data are prospectively recorded. The performance status was determined systematically in all patients with ECOG score and is used for estimating prognosis and defining therapeutic goals. Intraoperative data included peritoneal cancer index (PMI) [1], ascites, adhesiolysis, and operative time. Postoperative hospital stay and 30 day complications were recorded. The number of patients who completed all three PIPAC procedures and six cycles of IV chemotherapy is noted. The response assessment is performed using magnetic resonance imaging (MRI) scanning. All mortality events will be noted.

Study assessment and time points

The QoL assessment by Global Health Function Score and symptom scores of EORTC QLQ-C30(Version 3.0) questionnaire is performed before starting therapy and at 60, 120, and 180 days after the first intervention.

Primary endpoint

The proportion of patients with a deterioration of Global Health Function Score of more than 10 points 60, 120, and 180 days of EORTC QLQ-C30 after the first intervention.

Secondary endpoints

The number of patients who completed all three PIPAC procedures and six cycles of IV chemotherapy (Figure 1).

Pertinent demographic and surgical data are prospectively recorded. Intraoperative data included PMI [1], ascites, adhesiolysis, and operative time. Postoperative hospital stay and 30 day complications were recorded. The number of patients who completed all three PIPAC procedures and six cycles of IV chemotherapy are noted.

PIPAC procedure treatment algorithm

Surgical setup, treatment regimens, and safety checklist were adopted from recommendations by Solaß et al. [10, 15]. Three PIPAC treatments are scheduled at 6 week intervals after randomization. For patients with ovarian PM [16], pressurized aerosol of cisplatin 7.5 mg/m^2 in 150 mL NaCl 0.9 % solution followed by doxorubicin 1.5 mg/m^2 in 50 mL NaCl 0.9 % solution, and for gastric cancer and mesothelioma [17], a pressurized aerosol containing doxorubicin at a dose of 1.5 mg/m^2 body surface in a 50 mL NaCl 0.9 % solution followed by cisplatin at a dose of 7.5 mg/m^2 body surface in a 150 mL NaCl 0.9 % solution were applied via aerosoliser and injector. For colorectal and appendiceal cancer patients, oxaliplatin at a dose of 92 mg/m^2 was applied [18]. Systematically, thoracic and abdominal MRI is performed four weeks prior to the first PIPAC and between PIPAC#2 and PIPAC#3 at 12th week to rule out extraperitoneal disease. A third MRI is scheduled at 20 weeks after finishing PIPAC therapy. Every patient is seen in outpatient consultation 4 weeks after PIPAC treatment for monitoring of complications and evaluation to proceed with further PIPAC. QoL assessment is performed at start of treatment followed by at 60, 120, and 180 days (Figure 2). Reaction to treatment and side effects after each application are noted and graded as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [19]

Systemic IV chemotherapy treatment algorithm

Chemotherapy drugs, treatment regimens, and safety checklist are decided based on the primary pathology and history of previous chemotherapy. Six systemic IV chemotherapy treatments are scheduled at 3 week intervals after randomization. Systematically, thoracic and abdominal MRI is performed four weeks prior to the first cycle and between cycle#3 and cycle#4 at 12th week to rule out extraperitoneal disease. A third MRI is scheduled at 20 weeks after completion of treatment. Every patient is seen in outpatient consultation prior to start of each cycle with routine blood investigation for monitoring of complications and evaluation to proceed with further chemotherapy. QoL assessment is performed at start of treatment followed by at 60, 120, and 180 days (Figure 3). Reaction to treatment and side effects after each cycle are noted and graded as per CTCAE [19].

Statistical analysis

A descriptive statistical analysis is carried out and quantitative and qualitative data described according to means (±standard deviation),

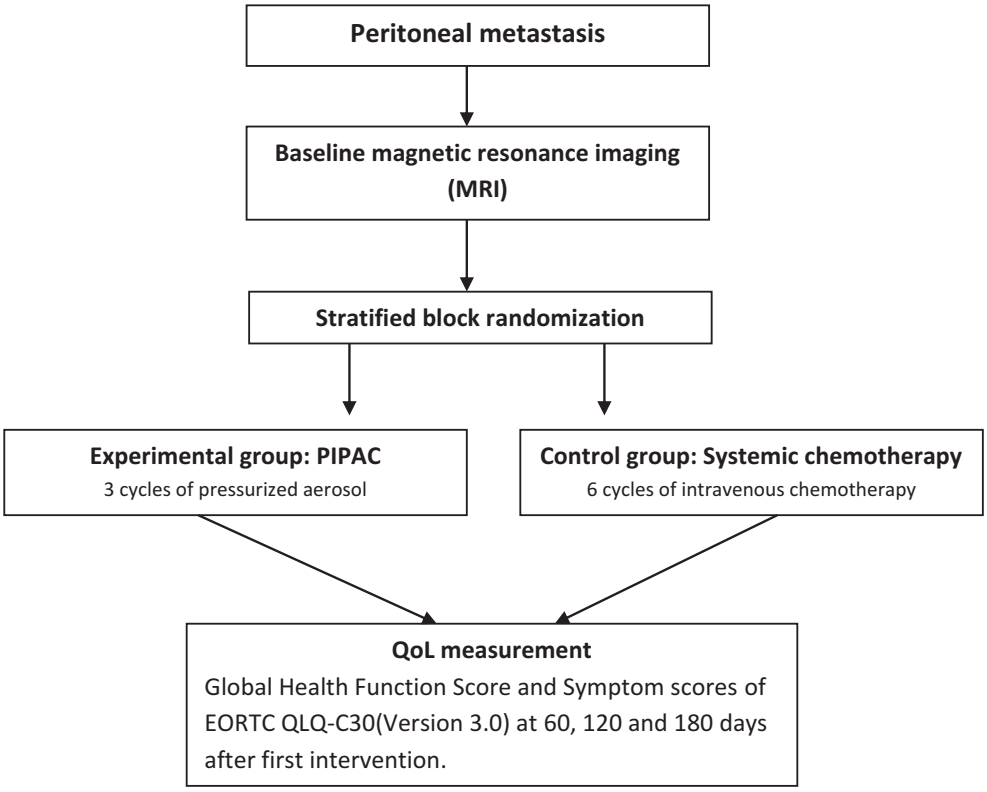

Figure 1: Intervention (experimental and control group including time point and technique of randomization).

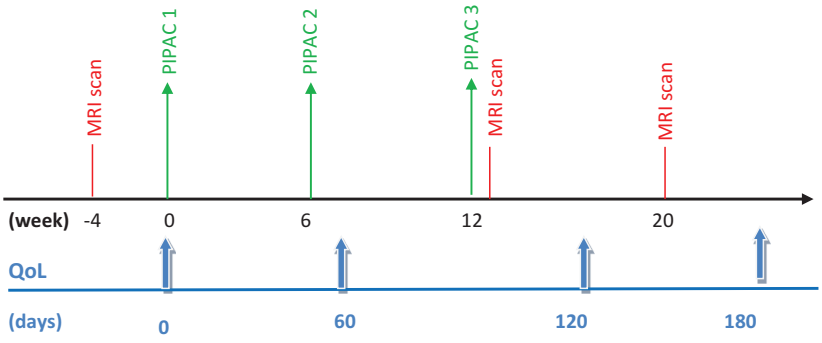

Figure 2: Treatment algorithm for pressurized intraperitoneal aerosol chemotherapy (PIPAC).
PIPAC treatment was scheduled as repeated application (3×) at 6 week intervals. Thoracic and abdominal magnetic resonance imaging (MRI) was performed 4 weeks prior to therapy, in between at 12 weeks, and after completion at 20 weeks to search for extraperitoneal disease. Quality of life (QoL) was systematically assessed (EORTC QLQC30) four times: prior to start of treatment and at 60, 120, and 180 days after start of treatment.

medians (range), and percentages. Collected data will be entered in excel software and analysed using R software version 3.4.4. Continuous variables are presented as mean with standard error of the mean or median with range or interquartile range as appropriate. Categorical variables will be presented as count and per cent. For statistical analysis, the 30 scores are linearly converted to a 0–100 scale according to EORTC recommendations [20–22]. Mean comparison of primary endpoint EORTC QLQ-30 between two groups will be done using independent t-test. All p-values of less than 0.05 are considered statistically significant.

For sample size calculation, primary endpoint EORTC QLQ-30 of Global Health Function Score was considered. The expected mean

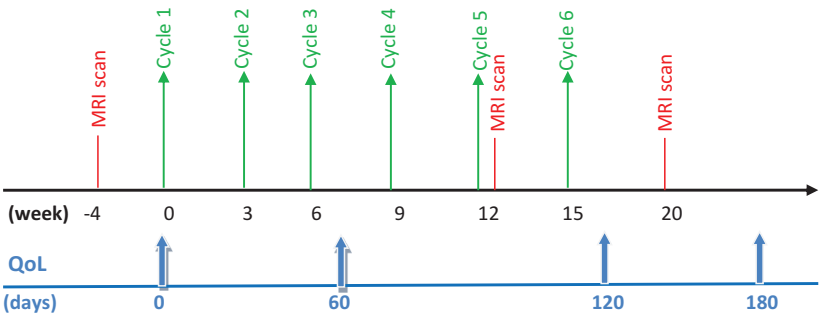

Figure 3: Treatment algorithm for intravenous (IV) chemotherapy.
IV chemotherapy treatment was scheduled as repeated application (6×) at 3 week intervals. Thoracic and abdominal magnetic resonance imaging (MRI) was performed 4 weeks prior to therapy, in between at 12 weeks, and after completion at 20 weeks to search for extraperitoneal disease. Quality of life (QoL) was systematically assessed (EORTC QLQC30) four times: prior to start of treatment and at 60, 120, and 180 days after start of treatment.

Physical function (PF) score in PIPAC group is 46 with standard deviation 39. Estimated effect size is 10. Using the following formula [23]:

$$n = \left(\sigma \frac{z_{1-\alpha/2} + z_{1-\beta}}{\mu_A - \mu_B}\right)^2$$

where
μ is expected mean time ($\mu_A = 46$ and $\mu_B = 56$)
σ is standard deviation = 39
α is type I error = 5 %
β is type II error, meaning 1–β is power = 80 %

In sample size calculation, the expected mean PF score in PIPAC group is 46 and expected mean PF score in the IV chemotherapy group is 56. Calculated sample size is 119 rounded to 120. In each treatment group, 60 subjects will be enrolled.

Outcome measures

Primary outcome measures:
1. Quality of life

Secondary outcome measures:
1. Morbidity
2. Mortality

Ethical approval and consent

Institutional Review Board approval for an off-label use programme of PIPAC in women with PM was obtained. Institutional Review Board number: ECR/34/KA/2013/RR-16; Date of approval: May 4, 2018; Reference number: REF/2018/08/021225. No individual person's data contained in the publication.

Discussion

PIPAC is easy to perform, well tolerated by most patients, and has shown promising response in women with end-stage PM. Good tolerance profile and QoL in PIPAC treatment can allow assessing bidirectional regimens combining systemic and intraperitoneal PIPAC treatment. Future prospective studies should present histological regression score results in comparison with QoL. Furthermore, PIPAC procedure and treatment algorithms need to be standardized for various pathologies.

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