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First-line palliative systemic therapy alternated with electrostatic pressurised intraperitoneal aerosol chemotherapy (oxaliplatin) for isolated unresectable colorectal peritoneal metastases: protocol of a multicentre, single-arm, phase II study (CRC-PIPAC-II)

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ABSTRACT

Introduction Despite its increasing use, first-line palliative systemic therapy alternated with electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin (ePIPAC-OX), hereinafter referred to as first-line bidirectional therapy, has never been prospectively investigated in patients with colorectal peritoneal metastases (CPM). As a first step to address this evidence gap, the present study aims to assess the safety, feasibility, antitumour activity, patient-reported outcomes, costs and systemic pharmacokinetics of first-line bidirectional therapy in patients with isolated unresectable CPM.

Methods and analysis In this single-arm, phase II study in two Dutch tertiary referral centres, 20 patients are enrolled. Key eligibility criteria are a good performance status, pathologically proven isolated unresectable CPM, no previous palliative systemic therapy for colorectal cancer, no (neo)adjuvant systemic therapy ≤6 months prior to enrolment and no previous pressurised intraperitoneal aerosol chemotherapy (PIPAC). Patients receive three cycles of bidirectional therapy. Each cycle consists of 6 weeks first-line palliative systemic therapy at the medical oncologists' decision (CAPOX-bevacizumab, FOLFOX-bevacizumab, FOLFIRI-bevacizumab or FOLFOXIRI-bevacizumab) followed by ePIPAC-OX (92 mg/m^2) with an intraoperative bolus of intravenous leucovorin (20 mg/m2) and 5-fluorouracil (400 mg/m^2). Study treatment ends after the third ePIPAC-OX. The primary outcome is the number of patients with—and procedures leading to—grade ≥3 adverse events (Common Terminology Criteria for Adverse Events V.5.0) up to 4 weeks after the last procedure. Key secondary outcomes include the number of bidirectional cycles in each patient, treatment-related characteristics, grade ≤2 adverse events, tumour response (histopathological, cytological, radiological, biochemical, macroscopic and ascites), patient-reported outcomes, systemic pharmacokinetics of oxaliplatin, costs, progression-free survival and overall survival.

Ethics and dissemination This study is approved by the Dutch competent authority, a medical ethics committee and the institutional review boards of both study centres. Results will be submitted for publication

Strengths and limitations of this study

- First prospective phase II study assessing the safety, feasibility and antitumour activity of first-line palliative systemic therapy with bevazicumab alternated with pressurised intraperitoneal aerosol chemotherapy (oxaliplatin) for colorectal peritoneal metastases (CPM).
- Inclusion of a clinically homogenous population of patients with CPM receiving first-line palliative treatment.
- Assessment of multiple secondary outcomes, for example, patient-reported outcomes, costs and the systemic pharmacokinetics of oxaliplatin.
- Translational side studies of the present study may open new opportunities for research in understanding and treating CPMs.
- Potential limitation: histopathological heterogeneity (ie, enrolment allowed for both appendiceal and colorectal primary tumours and signet ring cell carcinoma).

in peer-reviewed medical journals and presented to patients and healthcare professionals.
Trial registration number NL8303.

INTRODUCTION

The peritoneum is a common metastatic site in colorectal cancer, and the presence of colorectal peritoneal metastases (CPM) is characterised by a poor prognosis.[1 2] Most patients with CPM are treated with palliative intent.[3] When treated with systemic therapy, patients with CPM have a shorter survival than patients with systemic metastases of colorectal cancer.[4]

Theoretically, intraperitoneal chemotherapy could be an interesting palliative treatment option due to a favourable peritoneum–plasma concentration ratio.[5] However, the use of intraperitoneal chemotherapy is limited by poor direct tumour penetration, inhomogeneous intraperitoneal drug distribution and dose-limiting local toxicity.[6 7] Pressurised intraperitoneal aerosol chemotherapy (PIPAC) has been developed to overcome these limitations.[8–11] PIPAC is a laparoscopic method for the repetitive intraperitoneal administration of low-dose chemotherapy as a pressurised aerosol, claiming enhanced tumour penetration, homogeneous intraperitoneal drug distribution and low toxicity in preliminary studies.[8–11] The first clinical reports have suggested that PIPAC is feasible, safe and well tolerated in patients with peritoneal metastases of various primary tumours.[12 13] Given these results, PIPAC is currently implemented in a rapidly increasing number of centres worldwide.[12 14] In these centres, patients with CPM are generally treated with PIPAC with oxaliplatin (92 mg/m^2) every 6–8 weeks, with or without concomitant systemic therapy.[14] Electrostatic precipitation of the aerosol is thought to enhance tissue penetration and is practised in several centres.[15–18]

Previously, a multicentre, single-arm, phase II study (CRC-PIPAC) investigated the safety, feasibility antitumour activity, patient-reported outcomes (PROs), costs and pharmacokinetics of repetitive electrostatic PIPAC with oxaliplatin (ePIPAC-OX) as a palliative monotherapy in 20 patients with isolated unresectable CPM in any line of palliative treatment.[19 20]

Repetitive ePIPAC-OX could also be added to first-line systemic therapy with the aim to maximise intraperitoneal tumour response and eliminate systemic micrometastases. The combination of first-line systemic therapy (including bevacizumab) and repetitive ePIPAC-OX, hereinafter referred to as first-line bidirectional therapy, is already offered to patients with isolated unresectable CPM in several PIPAC centres worldwide.[14]

Despite its increasing use, the feasibility, safety and antitumour activity of first-line bidirectional therapy has never been prospectively investigated in patients with isolated unresectable CPM in clinical trials with predefined eligibility criteria, interventions and outcomes. Moreover, nothing is known about PROs and costs of—and the systemic pharmacokinetics of oxaliplatin during—first-line bidirectional therapy in this setting. As a first step to address this evidence gap, the present multicentre, single-arm, phase II study (CRC-PIPAC-II) aims to assess the safety, feasibility antitumour activity, PROs, costs and systemic pharmacokinetics of first-line bidirectional therapy in patients with isolated unresectable CPM.

METHODS AND ANALYSIS

Setting

This study is performed in two Dutch tertiary referral centres for the surgical treatment of CPM.

Eligibility criteria

Eligibility criteria are:

- ≥18 years of age.
- WHO performance status of 0–1.
- Histologically or cytologically proven peritoneal metastases of a colorectal or appendiceal carcinoma.
- Unresectable disease, defined as a Peritoneal Cancer Index (PCI) >20 or if complete resection of peritoneal metastases is surgically not feasible, based on abdominal CT, laparoscopy or laparotomy.
- Adequate organ functions (hemoglobin ≥5.0 mmol/L, neutrophils ≥1.5×10^9/L, platelets ≥100×10^9/L, serum creatinine <1.5 × upper limit of normal (ULN), creatinine clearance ≥30 mL/min and liver transaminases <5 × ULN).
- No symptoms of gastrointestinal obstruction.
- No systemic metastases.
- No contraindications for the planned systemic therapy or laparoscopy.
- No previous PIPAC.
- No previous palliative systemic therapy for colorectal cancer.
- No (neo)adjuvant systemic therapy for colorectal cancer ≤6 months prior to enrolment.

Interventions and procedures

The study flow chart is shown in figure 1. The schedule of enrolment, interventions and assessments is shown in table 1.

All patients receive three cycles of first-line bidirectional therapy. Each cycle consists of 6 weeks of first-line systemic therapy followed by one ePIPAC-OX. Study treatment ends after the third ePIPAC-OX in all patients.

First-line palliative systemic therapy

The treating medical oncologist determines which of the following first-line regimens will be used:

- Two 3-weekly cycles of CAPOX-bevacizumab (intravenous oxaliplatin (130 mg/m^2 body surface area (BSA)) on day 1, oral capecitabine (1000 mg/m^2 BSA) twice daily on days 1–14, intravenous bevacizumab (7.5 mg/kg body weight) on day 1).
- Three 2-weekly cycles of FOLFOX-bevacizumab (intravenous oxaliplatin (85 mg/m^2 BSA) on day 1, intravenous leucovorin (400 mg/m^2 BSA) on

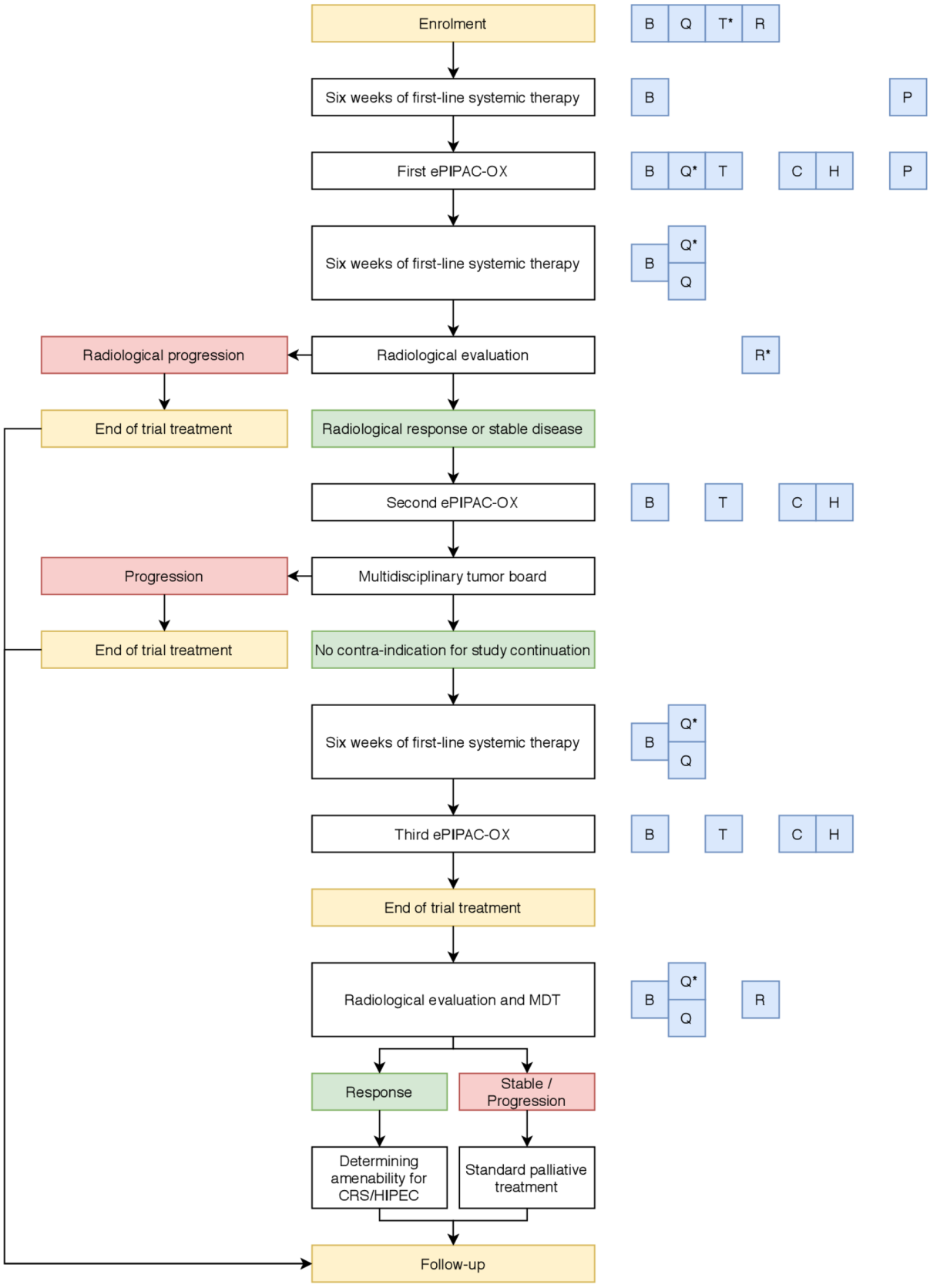

Figure 1 Study flow chart. B, bloods (organ functions and tumor markers); C, cytology (ascites or peritoneal lavage); CRS, cytoreductive surgery; ePIPAC-OX, electrostatic pressurized intraperitoneal aerosol chemotherapy with oxaliplatin; H, histopathology (peritoneal biopsies); MDT, multidisciplinary tumor board; HIPEC, hyperthermic intraperitoneal chemotherapy; P, pharmacokinetic sampling; Q, questionnaires (costs and patient-reported outcomes); Q*, questionnaires (patient-reported outcomes); R, radiology (thoracoabdominal CT and diffusion-weighted MRI peritoneum); R*, thoracoabdominal CT; T, translational research (blood and ascites or peritoneal lavage); T*, translational research (blood).

Table 1 Schedule of enrolment, interventions and assessments

	Enrolment	Baseline	First 6 weeks first-line systemic therapy	First ePIPAC-OX	Second 6 weeks first-line systemic therapy	Second ePIPAC-OX	Third 6 weeks first-line systemic therapy	Third ePIPAC-OX	Final evaluation	Follow-up
Enrolment										
Eligibility screen	×									
Informed consent	×									
Interventions										
Blood samples (organ functions and tumour markers)		×	×	×	×	×	×	×	×	
Thoracoabdominal CT		×			×*				×	
Diffusion-weighted MRI peritoneum		×							×	
Collection of ascites or peritoneal lavage				×		×		×		
Peritoneal biopsies				×		×		×		
Questionnaires: patient-reported outcomes		×	×†		×‡		×‡		×‡	
Questionnaires: Costs		×			×§		×§		×§	
Blood samples for pharmacokinetics			×	×						
Translational research (blood)		×		×¶		×¶		×¶		
Translational research (ascites or peritoneal lavage)				×		×		×		
Assessments										
Baseline characteristics		×								
Treatment-related characteristics (systemic therapy)			×		×		×			
Treatment-related characteristics (ePIPAC-OX)				×		×		×		
Adverse events			×	×	×	×	×	×	×	
Hospital stay				×		×		×		
Readmissions					×		×		×	
Clinical evaluation		×	×	×	×	×	×	×	×	

Continued

Table 1 Continued

	Enrolment	Baseline	First 6 weeks first-line systemic therapy	First ePIPAC-OX	Second 6 weeks first-line systemic therapy	Second ePIPAC-OX	Third 6 weeks first-line systemic therapy	Third ePIPAC-OX	Final evaluation	Follow-up
Biochemical response			×	×	×	×	×	×	×	
Radiological response					×*				×	
Histopathological response				×		×		×		
Cytological response				×		×		×		
Macroscopic response				×		×		×		
Ascites response				×		×		×		
Patient-reported outcomes		×	×†		×‡		×‡		×‡	
Costs		×			×§		×§		×§	
Progression-free survival			×	×	×	×	×	×	×	×
Overall survival			×	×	×	×	×	×	×	×

*1 week before the second ePIPAC-OX.
†1 week before the first ePIPAC-OX.
‡One and 4 weeks after ePIPAC-OX.
§4 weeks after ePIPAC-OX.
¶Just before ePIPAC-OX.
ePIPAC-OX, electrostatic pressurised intraperitoneal aerosol chemotherapy with oxaliplatin.

day 1, intravenous bolus/continuous 5-fluorouracil (400/2400 mg/m^2 BSA) on days 1–2, intravenous bevacizumab (5 mg/kg body weight) on day 1).

- Three 2-weekly cycles of FOLFIRI-bevacizumab (intravenous irinotecan [180 mg/m^2 BSA) on day 1, intravenous leucovorin (400 mg/m^2 BSA) on day 1, intravenous bolus/continuous 5-fluorouracil (400/2400 mg/m^2 BSA) on days 1–2, intravenous bevacizumab (5 mg/kg body weight) on day 1).
- Three 2-weekly cycles of FOLFOXIRI-bevacizumab (intravenous oxaliplatin (85 mg/m^2 BSA) on day 1, intravenous irinotecan (165 mg/m^2 BSA) on day 1, intravenous leucovorin (400 mg/m^2 BSA) on day 1, intravenous continuous 5-fluorouracil (2400 mg/m^2 BSA) on days 1–2, intravenous bevacizumab (5 mg/kg body weight) on day 1).

These regimens are based on the European Society for Medical Oncology (ESMO) and the Dutch guideline for the treatment of metastatic colorectal cancer.[21 22] According to the ESMO guideline, both bevacizumab and anti-EGFR therapy can be added to first-line systemic chemotherapy when disease control is the main goal of treatment. According to the Dutch guideline, bevacizumab is the first-choice biological agent for the treatment of metastatic colorectal cancer, as it can be administered to patients with wildtype KRAS and patients with mutated KRAS, in contrast to anti-EGFR therapy.

Dose reductions, switches between allowed regimens and management of toxicity are left to the discretion of the treating medical oncologist. Dihydropyrimidine dehydrogenase status is assessed by genotyping before the first administration of systemic therapy, and dosages of capecitabine or 5-fluorouracil are modified accordingly.[23]

ePIPAC-OX

The procedure has been extensively described in the protocol of the CRC-PIPAC study.[19 20] In summary, after creating a 12 mm Hg pneumoperitoneum with two balloon trocars using an open introduction, an explorative laparoscopy is performed with adhesiolysis if needed to create enough working space. If ePIPAC-OX seems feasible, leucovorin (20 mg/m^2 BSA in 10 min) and 5-fluorouracil (400 mg/m^2 BSA in 15 min) are administered intravenously, since these drugs are thought to increase the efficacy of oxaliplatin.[24 25] Meanwhile, ascites (or peritoneal lavage using saline if ascites is absent) is evacuated and sent for cytology, the PCI and ascites volume are registered[26] and three peritoneal metastases from different intra-abdominal areas (if possible) are biopsied and sent for histopathology. Biopsy locations are marked with clips to enable similar biopsies during subsequent procedures.

Then, after building the PIPAC setup and ensuring a leak-free pneumoperitoneum, oxaliplatin (92 mg/m^2 BSA (maximum 184 mg) diluted to a total volume of 150 mL in a 5% dextrose solution) is aerosolised into the peritoneal cavity through a nebuliser (CapnoPen, Capnomed GmbH, Villingendorf, Germany) using an angiographic injector at a maximum pressure of 200 psi and a flow of 30 mL/min, all according to internationally used protocols.[14] After formation of the aerosol in 5 min, it is electrostatically precipitated for another 25 min using Ultravision technology (Alesi Surgical, Cardiff, UK) as described by others,[16] as this could enhance tumour penetration of oxaliplatin.[15]

Then, the peritoneal cavity is exsufflated through a closed aerosol waste system, instruments are removed, and incisions are closed.

Postoperatively, patients receive analgesics and antiemetics according to local protocol. Standard postoperative clinical evaluations are performed a few hours after ePIPAC-OX and on every postoperative day until discharge. Postoperative laboratory tests are only performed if indicated. Patients are intentionally discharged on the day of ePIPAC-OX or on the first postoperative day.

Evaluations

Before each cycle of systemic therapy, patients undergo clinical and biochemical (ie, tumour markers and organ functions) evaluation by the treating medical oncologist. Before each ePIPAC-OX, patients undergo clinical evaluation by the treating surgeon. During and shortly after ePIPAC-OX, patients undergo macroscopic (ie, peritoneal cancer index (PCI)[26]) and ascites volume), histopathological (ie, peritoneal regression grading score (PRGS) of peritoneal biopsies[27 28]) and cytological evaluation. Radiological evaluation is performed 1 week before the second ePIPAC-OX and 4 weeks after the third ePIPAC-OX.[29] Patients are discussed by a multidisciplinary tumour board after the second and third ePIPAC-OX.

After completing 6 weeks of systemic therapy, the subsequent ePIPAC-OX is planned within 1–4 weeks thereafter. After ePIPAC-OX, systemic therapy is restarted 1–4 weeks postoperatively. Study treatment is discontinued in case of physician-determined disease progression, unacceptable toxicity or physician's or patient's decision to discontinue participation. Study treatment ends after the third ePIPAC-OX, regardless of response to therapy, after which patients receive standard supportive, palliative or curative care according to the Dutch national guideline without further ePIPAC-OX.[22]

Pharmacokinetic sampling

Four millilitres of whole blood samples are collected in heparin tubes at multiple time points during and after the first ePIPAC-OX as well as during and after the first cycle of systemic therapy:

- ePIPAC-OX: at t=0, t=0.5, t=1, t=2 and t=16 hours and t=1 week after intraperitoneal oxaliplatin injection.
- CAPOX-bevacizumab: at t=0, t=0.5, t=1 and t=2 hours and t=3 weeks after intravenous administration of oxaliplatin.
- FOLFOX-bevacizumab or FOLFOXIRI-bevacizumab: at t=0, t=0.5, t=1, t=2, t=48 hours and t=2 weeks after intravenous administration of oxaliplatin.

After direct centrifuging, a plasma aliquot is stored at −80°C until analysis. To obtain the free fraction of

oxaliplatin, a second 1 mL plasma aliquot is centrifuged through an ultrafiltration membrane and stored at −80°C until analysis. Oxaliplatin concentrations are measured using atomic absorption spectrometry performed on a Thermo Fisher Solaar ICE 3500 graphite-furnace spectrophotometer with Zeeman correction (Thermo Fisher Scientific, Bremen, Germany).

Translational research

Two 10 mL cell-free DNA BCT tubes (Streck, La Vista, Nebraska, USA) are used to collect 20 mL of whole blood at baseline and before each ePIPAC-OX. Tubes are sent to a central laboratory for isolation and storage (−80°C) of plasma and cell pellet according to the manufacturer's instructions. Collected ascites or peritoneal lavage is centrifuged twice (5 min, 420 g, zero break) under sterile conditions. The supernatant is snap frozen and stored (−80°C) until further analysis. The cell pellet is suspended into an organoid culture medium at 4°C for transport and further preparation.

Outcomes

The primary outcome is the number of patients with—and procedures leading to—grade ≥3 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0 (primary classification) and Clavien-Dindo (secondary classification) up to 4 weeks after the last ePIPAC-OX.[30 31]

Secondary outcomes are:

- The number of completed cycles of bidirectional therapy in each patient and reasons for discontinuation.
- Characteristics of systemic therapy (eg, administered regimens, number of completed cycles and dose reductions).
- Characteristics of ePIPAC-OX (eg, intraoperative complications and operating time).
- The number of patients with—and procedures leading to—grade ≤2 adverse events according to the CTCAE V.5.0 (primary classification) and Clavien-Dindo (secondary classification) up to 4 weeks after the last ePIPAC-OX.[30 31]
- Hospital stay, defined as the number of days between ePIPAC-OX and initial discharge.
- Readmissions, defined as any unplanned hospital admission after initial discharge up to 4 weeks after the last ePIPAC-OX.
- Radiological tumour response, centrally evaluated by two assessors blinded to clinical outcomes, using the Response Evaluation Criteria In Solid Tumors V.1.1 and the radiological PCI.[29]
- Histopathological tumour response, centrally evaluated by two assessors blinded to clinical outcomes, using the four-tier PRGS of collected peritoneal biopsies during each ePIPAC-OX.[27 28]
- Macroscopic tumour response, based on the PCI during each ePIPAC-OX.
- Ascites response, based on ascites volume during each ePIPAC-OX.
- Biochemical tumour response, based on carcinoembryonic antigen levels at baseline and before each ePIPAC-OX.
- Cytological tumour response, based on the presence or absence of malignant cells in ascites or peritoneal lavage collected during each ePIPAC-OX.
- PROs, based on the EQ-5D-5L,[32] EORTC QLQ-C30[33] and EORTC QLQ-CR29[34] questionnaires at baseline, 1 week before the first ePIPAC-OX and 1 and 4 weeks after each ePIPAC-OX.
- The bioavailability of oxaliplatin, based on the systemic pharmacokinetics of oxaliplatin during and after one intravenous administration, as well as during and after one ePIPAC-OX.
- Costs, derived from the Dutch cost guideline for healthcare research at the time of analysis, based on hospital information systems, case report forms and the iMTA Productivity cost questionnaire[35] and the iMTA Medical consumption questionnaire[36] at baseline and 4 weeks after each ePIPAC-OX.
- Progression-free survival, defined as the time between enrolment and physician-determined disease progression or death.
- Overall survival, defined as the time between enrolment and death.

Sample size

Given the absence of data to guide a sample size calculation, the central ethics committee approved a pragmatically determined sample size of 20 patients as a sufficient number to explore the safety, feasibility and antitumour activity of the study treatment, similar to the CRC-PIPAC study.[19 20] Enrolled patients who are unable to receive the first ePIPAC-OX are replaced to enrol a total number of 20 patients who receive at least one cycle of bidirectional therapy.

Recruitment

The study commenced on 30 January 2020 and the first patient was enrolled on 5 February 2020. The investigators expect to complete accrual within a maximum of 3 years. Strategies for achieving adequate patient accrual are not defined a priori.

Data collection and data management

Outcomes are collected in all patients who complete at least one cycle of bidirectional therapy. All baseline characteristics and outcomes are prospectively collected by a local investigator in each study centre using standardised electronic case report forms linked to an ISO 27001 certified central study database (De Research Manager, Deventer, the Netherlands). This ISO 27001 certified system optimises data quality by standardised data entry, coding, security and storage.

Statistical methods

Continuous data are presented as a median with (interquartile) range, and categorical data are presented as

number (percentage). Due to the single-arm design of the present study and the explorative nature of the analysed outcomes, basic statistical methods are not defined a priori. These methods will be defined before data analysis. Time-to-event variables, such as progression-free and overall survival, are analysed and presented using the Kaplan-Meier method.

Data monitoring

Interim analyses are performed 4 weeks after the 5th, 15th, 30th and 45th procedure. The study is terminated, or temporarily halted for evaluation and potential adaption of the study protocol, if more than three CTCAE grade 3 or 4 adverse events occur or more than one CTCAE grade 5 adverse event occur that are considered directly related to ePIPAC-OX. Adverse events related to systemic therapy are not included in the stopping rules. If the study is terminated, enrolled patients do not receive any further ePIPAC-OX. The principal investigators (IHJTH and DB) have access to the interim results and make the final decision to terminate or continue the study. No data monitoring committee was formed for this study.

Harms

All serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) that occur from enrolment up to 4 weeks after the last ePIPAC-OX are reported by local investigators to the coordinating investigator within 24 hours. The coordinating investigator reports these SAEs/SUSARs to the central ethics committee within 7 days of first knowledge for lethal or life-threatening SAEs/SUSARs and within 15 days for other SAEs/SUSARs.

Auditing

Auditing is performed by independent qualified monitors of the study centres. The study is considered a medium-risk study according to the brochure 'Kwaliteitsborging mensgebonden onderzoek 2.0' by the Dutch Federation of University Medical Centers, meaning that study centres are audited two to three times per year, depending on enrolment, with 25% auditing of the study master file, investigator site files, informed consent forms, eligibility criteria, source data verification and SAEs/SUSARs.

Patient and public involvement

Patients are not involved in the design, recruitment and conduct of the study but will be involved in the dissemination of study results.

ETHICS AND DISSEMINATION

Research ethics approval

The present study is approved by a central ethics committee (MEC-U, Nieuwegein, Netherlands, number R19.087) and the institutional review boards of both study centres.

Protocol amendments

Important modifications to the study protocol need to be authorised by the central ethics committee. After authorisation, these modifications are communicated to the Dutch competent authority, the institutional review boards of both study centres, all investigators, study registries and patients (if required by the central ethics committee).

Informed consent

Patients are enrolled by their treating physician and provide written informed consent. Patients are able to give separate consent for participation in translational side studies.

Confidentiality

Personal data of patients is collected, shared and maintained according to the Dutch law.

Access to data

All authors have access to the final dataset, without any contractual agreements that limit such access.

Ancillary and poststudy care

One of the study centres (Catharina Hospital, Eindhoven, the Netherlands) is insured to cover harms caused by study participation in either participating hospital. After stopping study treatment, patients receive further supportive, palliative or curative intent treatment according to Dutch guideline.[22]

Dissemination policy

Study results will be personally communicated to participants, submitted for publication in peer-reviewed medical journals and presented to patients, healthcare professionals and the public during (inter)national meetings. Authorship eligibility guidelines are not defined a priori. The full study protocol and the Dutch informed consent form are available from the corresponding author. After study completion, the participant-level dataset and statistical code will be available on reasonable request.

DISCUSSION

To the knowledge of the authors, CRC-PIPAC-II is the first study that prospectively investigates the safety, feasibility, antitumour activity, PROs, costs and systemic pharmacokinetics of first-line systemic chemotherapy and bevacizumab alternated with repetitive ePIPAC-OX (ie, first-line bidirectional therapy) in patients with isolated unresectable CPM.

The present study has several strengths. All patients in the present study receive standard first-line systemic regimens based on the ESMO guideline for the treatment of metastatic colorectal cancer,[21] which contrasts the heterogeneity in treatment lines in available studies on (e) PIPAC-OX for CPM. The homogeneity in first-line treatment may facilitate a comparison between the present study and other first-line studies in metastatic colorectal

cancer. Furthermore, assessment of outcomes such as PROs, costs and systemic pharmacokinetics will provide further insight in the tolerability, costs and pharmacokinetic profile of first-line bidirectional therapy in this setting. Translational side studies may open new opportunities for research in understanding and treating CPM.

A potential limitation of the present study is the histopathological heterogeneity of the study population, since the eligibility criteria allow the enrolment of patients with both colorectal and appendiceal carcinomas, as well as including distinct pathological features such as signet ring cell histology. Furthermore, different first-line palliative systemic regimens are allowed, including FOLFOXIRI-bevacizumab, which might result in clinical heterogeneity. Although the potential clinical and histopathological heterogeneity could impede the interpretation of preliminary efficacy outcomes, this is not the major focus of this study.

With regards to the chemotherapy regimen used in this study, the results of the recently published PRODIGE-7 trial may question the intraperitoneal use of oxaliplatin (combined with 5-fluorouracil and leucovorin) in patients with CPM.[37] However, in contrast with PRODIGE-7, patients in the present study are either systemic therapy-naïve or had undergone a mandatory 6-month wash-out period of systemic therapy. As a result, the previously untreated patients in this study may be more sensitive to intraperitoneal oxaliplatin than patients in the PRODIGE-7 trial.

Most importantly, patients in the present study undergo palliative instead of curative intent treatment and receive repetitive instead of a single administration of intraperitoneal oxaliplatin. Repetitive PIPAC-OX (with or without intraoperative intravenous bolus 5-fluorouracil/leucovorin) is increasingly offered and frequently combined with first-line systemic chemotherapy and bevacizumab in many centres worldwide.[12 14 38 39] Despite the increasing use, the safety and feasibility of this combination has never been prospectively investigated in clinical trials. Altogether, it remains important to assess the feasibility and safety of the combination of first-line palliative systemic therapy and repetitive PIPAC-OX, hence the major focus of this study.

With regards to the oxaliplatin dose during PIPAC, two phase I dose-escalation trials recently assessed the maximum tolerated dose of repetitive PIPAC-OX for unresectable peritoneal metastases of various origins.[40 41] The French PIPOX trial observed two dose-limiting toxicities of systemic therapy with repetitive PIPAC-OX at 140 mg/m^2 and the investigators defined a maximum tolerated dose of repetitive PIPAC-OX of 90 mg/m^2. The PIPAC-OX trial from Singapore reported no dose-limiting toxicities with repetitive PIPAC-OX 120 mg/m^2 monotherapy; however, this trial was prematurely terminated due to the dose-limiting toxicities of the PIPOX trial. As a result, both trials are currently recruiting phase II expansion cohorts to investigate various systemic regimens combined with repetitive PIPAC-OX at 90 mg/m^2: a dose similar to the oxaliplatin dose in the current trial.

Results of several other ongoing single-arm, phase II studies are closely monitored. The first study primarily assesses the histopathological response of PIPAC with various drugs for peritoneal metastases of various origins (including PIPAC-OX for CPM), with or without concomitant systemic therapy, in 137 patients in any line of palliative treatment.[42] The second study assesses the safety of PIPAC with various drugs for peritoneal metastases of various origins (including PIPAC-OX for CPM), with or without concomitant systemic therapy, in 16 patients in a later line of palliative treatment (ClinicalTrials.gov, NCT04329494). The third study assesses progression-free survival of 30 patients with CPM receiving PIPAC-OX, with or without concomitant systemic therapy, in any line of palliative treatment (ClinicalTrials.gov, NCT03868228). Results of the previous CRC-PIPAC study, the present CRC-PIPAC-II study, and these ongoing studies may help designing future randomised trials to determine the role of (e)PIPAC-OX in the palliative treatment of patients with isolated unresectable CPM.

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