Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis

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Background: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a minimally invasive approach under investigation as a novel treatment for patients with peritoneal carcinomatosis of various origins. The aim was to review the available evidence on mechanisms, clinical effects and risks.

Methods: This was a systematic review of the literature on pressurized intraperitoneal chemotherapy published between January 2000 and October 2016. All types of scientific report were included.

Results: Twenty-nine relevant papers were identified; 16 were preclinical studies and 13 were clinical reports. The overall quality of the clinical studies was modest; five studies were prospective and there was no randomized trial. Preclinical data suggested better distribution and higher tissue concentrations of chemotherapy agents in PIPAC compared with conventional intraperitoneal chemotherapy by lavage. Regarding technical feasibility, laparoscopic access and repeatability rates were 83–100 and 38–82 per cent. Surgery-related complications occurred in up to 12 per cent. Postoperative morbidity was low (Common Terminology Criteria for Adverse Events grade 3–5 events reported in 0–37 per cent), and hospital stay was about 3 days. No negative impact on quality of life was reported. Histological response rates for therapy-resistant carcinomatosis of ovarian, colorectal and gastric origin were 62–88, 71–86 and 70–100 per cent respectively.

Conclusion: PIPAC is feasible, safe and well tolerated. Preliminary good response rates call for prospective analysis of oncological efficacy.

Paper accepted 1 February 2017

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.10521

Introduction

Peritoneal carcinomatosis remains a diagnostic and therapeutic challenge, and the prognosis for most underlying pathologies is dismal^{1–3}. Although systemic chemotherapy has allowed tremendous improvements in the treatment of systemic metastases (especially liver and lungs), it appears to be much less effective for peritoneal spread mainly owing to pharmacokinetic limitations⁴, probably because of poor peritoneal vascularization impeding proper drug distribution⁵. Cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) seems promising in highly selected patients⁶.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been proposed as a novel minimally invasive treatment for patients with advanced peritoneal carcinomatosis. PIPAC combines the benefits of a minimally

invasive approach (easier repeat application, lower morbidity, better quality of life (QoL)) with the pharmacokinetic advantages of intraperitoneal administration (higher intratumoral concentrations, less systemic toxicity) and pressurized vaporization (better distribution and penetration)^{7–10}. The aim of the present study was systematically to review the scientific evidence on PIPAC with regard to mechanism, pharmacokinetics, safety and clinical effects.

Methods

Data sources and search strategies

Main electronic databases including MEDLINE (searched through PubMed), Embase, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials were searched. The medical

subject heading (MeSH) terms used for searching PubMed were '(Intraperitoneal AND chemotherapy AND pressurized)'.

Further articles were sought by hand-searching electronic links to related articles and cross-referencing of selected articles. The trial registries <http://clinicaltrials.gov>, <http://clinicaltrial.org>, <http://isrctn.org>, <http://actr.org.au>, <http://trialregister.nl> and <http://www.umin.ac.jp/ctr> were screened for relevant unpublished prospective trials. The first description of a device to create intraperitoneal capnoperitoneum was published in 2000¹¹. Therefore, the search was limited to studies published between January 2000 and October 2016.

Study selection (inclusion and exclusion criteria)

All types of original scientific report were considered. Reviews and book chapters were excluded. No language restrictions were applied. Only studies on *pressurized* intraperitoneal chemotherapy were included. Excluded from the analysis were reports on intraperitoneal chemotherapy by conventional lavage (HIPEC) or by use of an intraperitoneal catheter. The included articles were divided into preclinical and clinical studies.

Data extraction and quality assessment

Pertinent study characteristics (prospective *versus* retrospective, sample size, control group) were defined *a priori* and each article was assessed for potential sources of bias. Three authors independently performed the literature search. The search terms were identified first in the title, and then in the abstract or MeSH. All studies of interest were obtained as full-text articles and scrutinized thoroughly. The entire research team made the final decision on inclusion of each study. Relevant data were extracted and documented in a database developed *a priori*. The following items were recorded: authors, title, year of publication, primary cancer, number of patients, number of PIPAC procedures, combination with other therapies, previous treatments, and surgical data (rate of non-access, surgery-related complications). Postoperative outcome measures were toxicity (assessed using the Common Terminology Criteria for Adverse Events, CTCAE)¹², complications, mortality and follow-up. Tumour response was evaluated when possible by means of the objective tumour response (assessed using the revised Response Evaluation Criteria in Solid Tumours, RECIST)¹³, histological response, and overall and disease-specific survival. Tumour response (efficacy) was assessed consistently in patients who received at least one cycle of the study

medication. Data are presented in accordance with the PRISMA statement¹⁴.

Data analysis

Statistical meta-analysis was not feasible as the original data were limited and heterogeneous. Therefore, descriptive statistics were applied and the available information was summarized in table form to provide a comprehensive overview of the most relevant aspects of mechanisms and clinical effects.

Results

The electronic search of the literature yielded 34 potential studies. By cross-referencing, 12 further studies were found. Of these 46 studies, five were excluded based on the title or abstract. Forty-one studies were evaluated as full-text articles. Of these, 12 were subsequently excluded owing to patient overlap or lack of new information: eight reviews^{15–22}, a textbook²³ and a book chapter²⁴. Two further studies were excluded owing to double publication: one²⁵ reporting on safety aspects in German, which duplicated information in a paper from the same group written in English²⁶, and one retrospective analysis²⁷ of the whole Herne cohort with patient overlap with other publications from the same group (Fig. 1). MEDLINE search (PubMed) revealed most included articles; other data sources provided additional studies that were not indexed in PubMed^{28,29}. Twenty-nine studies were retained for final analysis, 16 preclinical studies and 13 clinical reports (Tables 1 and 2)^{7–11,26–49}. Of note, 23 of the 29 studies were performed by one working group from the pioneer centre in Herne, Germany; the remaining reports came from five other institutions.

Of the preclinical studies, 11 were animal studies, using *in vivo* (7) or *ex vivo* (4) models; all except two^{30,31} were porcine models. Two experimental studies^{33,38} dealt with human tissue samples and one study⁴⁰ performed *ex vivo* granulometric analysis. One publication²⁹ presented novel guidelines for histological tumour regression grading, and another study²⁶ evaluated health aspects.

Clinical publications included 801 PIPAC procedures and 12 different primary tumours in 346 patients overall (Table 2). Five^{10,28,42,44,45} were prospective studies, including one phase II trial⁴⁵, whereas six^{8,9,27,46,48,49} were conducted retrospectively. There were also two case reports^{43,47}. No RCT has been conducted so far. Evidence for gynaecological, gastric and colorectal cancers is summarized in Table 3, along with limitations and potential biases owing to combined treatments.

Fig. 1 PRISMA flow chart showing selection of articles for review

Preclinical data

Development of the concept

Three studies^{30–32} described the concept of intraperitoneal application of cytostatic solutions in gaseous form under pressure. A device to create therapeutic capnoperitoneum was first described in 2000¹¹, but technical limitations prevented clinical application. A novel device to overcome these technical issues was presented a decade later⁷. Biodistribution of molecules applied by PIPAC and conventional lavage (HIPEC model) was then tested in an *ex vivo* study³³. In the aerosolized specimen, the test substance was found to be biologically active up to 1 mm depth, and showed more activity in tumour nodules than in normal peritoneum, whereas no activity was detected in the lavage samples³³.

Conflicting results were reported by four recent studies^{37,39–41} on spatial drug distribution and tissue concentrations of PIPAC. First, doxorubicin was aerosolized within a hermetic container system with tissue samples at different locations³⁷. Doxorubicin concentrations depended on location and were significantly higher at sites exposed directly to the aerosol jet of the nebulizer than at more distant sites⁴¹. Granulometric analysis under similar non-anatomical *ex vivo* conditions suggested a high percentage of droplets larger than 3 µm favouring gravitational deposition close to the nebulizer, instead of homogeneous drug distribution⁴⁰. Another similar experiment in the peritoneal cavity of a post-mortem swine simulated clinical conditions more precisely and reported more general dispersion of the drug, with penetration

depths between 350 µm in the centre and up to 150 µm in more distant sites³⁹.

Technique

Surgical technique was standardized by the pioneer group^{10,33} and conditions for PIPAC were defined empirically. Two balloon trocars (5 and 12 mm) were inserted using an open technique or Veress needle to create a 12 mmHg carbon dioxide capnoperitoneum. Alternatively, an Italian group⁸ described a single-port platform instead. Diagnostic laparoscopy included documentation of the extent of peritoneal carcinomatosis^{50,51}. After removing the ascites, punch biopsies and peritonectomy specimens were retrieved for pathological examination. The nebulizer was then inserted via the 10-mm trocar into the tight abdomen (as documented by zero-flow carbon dioxide) and connected to the pressure injector charged with liquid cytostatic solution. Oxaliplatin at a dose of 92 mg/m² of body surface in 150 ml dextrose solution was proposed for peritoneal carcinomatosis of colorectal origin. For peritoneal carcinomatosis of non-colorectal origin, a combination of cisplatin (7.5 mg/m² in 150 ml 0.9 per cent sodium chloride) and doxorubicin (1.5 mg/m² in 50 ml 0.9 per cent sodium chloride) was used. Conditions of nebulization were: application of cytostatics at a flow rate of 30 ml/min, a pressure of 1380 kPa over 30 min, at room temperature (22°C). After 30 min, the capnoperitoneum was evacuated by use of a closed-loop system through microparticle filters into the air waste system of the hospital.

Whenever feasible, at least three cycles were performed at 6-week intervals.

Safety strategy and workplace measurements

A stringent occupational health safety policy was elaborated by the German pioneer group²⁶. Briefly, three different levels of containment were proposed, namely air-tight pneumoperitoneum (balloon trocars, zero flow); laminar air flow and dilution capacity of the operating room; and remote application of cytostatics from outside the operating room. Air contamination levels were measured under clinical conditions while applying PIPAC in two patients. No leakage occurred, and no air contamination by cisplatin could be detected under real working conditions, both in surgeon and anaesthetist working positions. The tests were compliant with European Community safety law and regulations.

Potential chemopotentiating combinations

To combine the effects of PIPAC with hyperthermia, a Korean group³⁴ developed a device to test the feasibility of hyperthermic PIPAC in five pigs. The device was coupled

Table 1 Characteristics of preclinical studies

Reference	Study type	Primary tumour	Model	Research question	Outcome/conclusions
Jacquet <i>et al.</i> ³⁰	Experimental	n.a.	<i>In vivo</i> rat	Influence of increasing intra-abdominal pressure on tissue distribution and penetration	Increased tissue uptake in bladder, diaphragm and abdominal wall
Reymond <i>et al.</i> ¹¹	Experimental	n.a.	<i>In vivo</i> porcine	Development of a device to create therapeutic capnoperitoneum	Distribution in entire peritoneal surface; better tissue penetration under pressure
Esquis <i>et al.</i> ³¹	Experimental comparative	CRC	<i>In vivo</i> rat + porcine	Influence of increasing intra-abdominal pressure on penetration and antitumour effectiveness	Increased tumour accumulation and antitumour effect with manageable tolerance
Facy <i>et al.</i> ³²	Experimental comparative	CRC	<i>In vivo</i> porcine	Effect of hyperthermia and high pressure on blood and tissue absorption of oxaliplatin	Combination achieves highest tissue concentration, no increased systemic absorption
Solass <i>et al.</i> ³³	Proof of concept/ experimental	EC	<i>Ex vivo</i> human	Combination of Dbait and capnoperitoneum to evaluate biodistribution and tumour penetration	Enhanced penetration; CO ₂ as carrier ensures drug distribution, excellent intracellular uptake
Solass <i>et al.</i> ⁷	Technical note/ experimental	n.a.	<i>In vivo</i> porcine	Development of a device and comparison with conventional peritoneal lavage	Distribution and penetration significantly improved compared with peritoneal lavage
Solass <i>et al.</i> ²⁶	Experimental/ case series	n.a.	2 patients	Occupational health and safety aspects	Safety measures sufficient within specified study conditions; no occupational health hazards
Jung <i>et al.</i> ³⁴	Experimental	n.a.	<i>In vivo</i> porcine	Feasibility and safety of application of hyperthermic PIPAC (38.8–40°C)	Steady hyperthermic capnoperitoneum achieved. Feasible and safe.
Kakchekeeva <i>et al.</i> ³⁵	Experimental comparative	n.a.	<i>In vivo</i> porcine	Investigation of ePIPAC for enhancement of tissue uptake and distribution of tracer	Technically feasible, improved tissue uptake of tracers up to tenfold
Solass <i>et al.</i> ²⁹	Guidelines	n.a.	n.a.	Development of uniform terminology/grading of histological tumour response	Proposal of PRGS; needs external validation
Khosrawipour <i>et al.</i> ³⁶	Experimental	n.a.	<i>Ex vivo</i> porcine	Impact of irradiation on tissue penetration depth of doxorubicin during PIPAC	Higher (fractional) radiation might reduce penetration depth. Needs further evaluation
Khosrawipour <i>et al.</i> ³⁷	Experimental	n.a.	<i>Ex vivo</i> porcine	Exploration of spatial drug distribution and penetration pattern of doxorubicin	Heterogeneous spatial drug distribution, penetration highest in centre of aerosol jet spray
Reznicek <i>et al.</i> ³⁸	Retrospective	58 OC, 3 EC, 1 PMP, 1 GC	<i>Ex vivo</i> biopsies	Analysis of gene expression changes during PIPAC with doxorubicin and cisplatin	Changes in gene expression patterns during repeated PIPAC prognostic of overall survival
Khosrawipour <i>et al.</i> ³⁹	Experimental	n.a.	<i>Ex vivo</i> porcine	Exploration of spatial drug distribution pattern of doxorubicin in post-mortem swine	Doxorubicin reaches all areas in peritoneum; highest penetration around jet spray (350 µm)
Göhler <i>et al.</i> ⁴⁰	Experimental	n.a.	<i>Ex vivo</i> analysis	Technical description of MIP® and granulometric characterization of applied aerosol	Aerodynamics and large droplet size (> 3 µm) impede homogeneous drug distribution
Khosrawipour <i>et al.</i> ⁴¹	Experimental	n.a.	<i>Ex vivo</i> porcine	Influence of changes in pressure, distance of MIP® and doxorubicin concentration on penetration	Increased with higher drug concentration and closer MIP®, but not with higher pressure

n.a., Not available; CRC, colorectal cancer; EC, endometrial cancer; Dbait, DNA repair inhibitor; PIPAC, pressurized intraperitoneal aerosol chemotherapy; ePIPAC, electrostatic precipitation as an adjunct to PIPAC; PRGS, Peritoneal Regression Grading Score; OC, ovarian cancer; PMP, pseudomyxoma peritonei; GC, gastric cancer; MIP®, microinjection pump (Reger Medizintechnik, Villingendorf, Germany).

Table 2 Characteristics of clinical studies

Reference	Study design	No of patients (M:F)	No. of PIPAC procedures	Primary tumour	Failed access (%)	Histological response (%)‡	Surgery-related complications	Toxicity (grade 1/2/3/4/5)§	Follow-up*	Survival*
Giger-Pabst <i>et al.</i> ²⁸	Prospective case series	10	22	GC	n.a.	PP: 100 ITT: 70	9	n.a./n.a./1/0/1	n.a.	> 300 days¶
Blanco <i>et al.</i> ⁴²	Prospective phase 0 (toxicity) study	3 (2:1)	8	1 OC, 1 GC, 1 AC	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Tempfer <i>et al.</i> ⁴³	Case report	1 (0:1)	3	PMP	0	Yes	0	3/3/0/0/0	6 months	n.a.
Tempfer <i>et al.</i> ⁴⁴	Prospective case series	21 (0:21) (+8 CRS)	34	16 OC, 4 PPC, 1 FTC	14	PP: 75	12	12/0/3/2/0	192 days	442 days†
Solass <i>et al.</i> ¹⁰	Prospective case series	3 (2:1)	12	1 GC, 1 AC, 1 OC	0	100 (2 complete, 1 partial)	8	1/3/0/1/0	567 days	288 days†
Odendahl <i>et al.</i> ⁹	Observational, retrospective	91 (51:40)	158	29 GC, 25 OC, 14 CRC, 6 AC, 4 M, 6 CUP, 7 others	5.5	n.a.	3 (2)	n.a./n.a./8/1/3	12 months†	13.4 months
Tempfer <i>et al.</i> ⁴⁵	Phase II trial	53 (0:53)	130	47 OC, 4 PPC, 2 FTC	17	PP: 76–88 ITT: 62–72	4 (3)	71/32/8/0/0	n.a.	331 days†#
Tempfer <i>et al.</i> ⁴⁶	Cohort study	99 (0:99)	252	84 OC, 6 PPC, 3 CC, 3 EC, 1 BC, 1 PMP, 1 FTC	17	76	5 (2)	57/60/17/3/0	126 days	14.1 months
Giger-Pabst <i>et al.</i> ⁴⁷	Case report	1 (0:1)	8	OC	0	Yes	0	8/8/0/0/0	15 months	n.a.
Robella <i>et al.</i> ⁸	Retrospective	14	40	6GC, 3 OC, 2 CRC, 2 M, 1 PMP	2	n.a.	0	6/8/0/0/0	n.a.	n.a.
Nadiradze <i>et al.</i> ⁴⁸	Retrospective	24 (12:12)	60	GC	8	PP: 71	3 (5)	15/0/6/1/2	248 days	15.4 months
Demtröder <i>et al.</i> ⁴⁹	Retrospective	17 (10:7)	42	CRC	13	71–86	0	n.a./n.a./4/0/0	22 months†	15.7 months†
Girshally <i>et al.</i> ²⁷	Retrospective	9	32	6 CRC + AC, 1 OC, 1 M, 1 PMP	n.a.	78–89	n.a.	n.a.	n.a.**	n.a.**

Values in parentheses are percentages unless indicated otherwise; *values are median, except †mean. ‡Histological response in patients who had at least one cycle of the study medication. §Common Terminology Criteria for Adverse Events grades. ¶Patients with distant metastases (30 per cent) excluded. #Intention-to-treat (ITT) analysis (mean 407 days in per-protocol (PP) analysis). **All patients had cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy after neoadjuvant pressurized intraperitoneal aerosol chemotherapy (PIPAC). GC, gastric cancer; n.a., not available; OC, ovarian cancer; AC, appendiceal cancer; PMP, pseudomyxoma peritonei; PPC, primary peritoneal cancer; FTC, fallopian tube cancer; CRC, colorectal cancer; M, mesothelioma; CUP, cancer with unknown primary; CC, cervical cancer; EC, endometrial cancer; BC, breast cancer.

to heating units to achieve an effective temperature of 40°C. The test procedures could be performed safely under these conditions, and all pigs survived for 7 days until autopsy, which showed no thermal injury to the stomach, peritoneum or jejunum.

PIPAC was combined with irradiation in an *ex vivo* porcine model to evaluate a potential combined therapy³⁶. Irradiation with high (fractional) radiation reduced the tissue penetration depth of doxorubicin, whereas a low (fractional) radiation dose did not.

The ability of electrostatic precipitation to enhance the physical properties of gas and pressure was evaluated³⁵.

Electrostatic precipitation was achieved using a brush electrode for electrostatic loading of therapeutic aerosol, allowing tenfold improved tissue uptake of two tracer substances during PIPAC.

Clinical experience

Feasibility and safety

Clinical experience with PIPAC is summarized in Tables 2 and 3. Rates of failed access (unsuccessful procedures/attempted procedures) varied between 0 and 17 per cent. Surgery-related complications were observed in

Table 3 Clinical results of studies reporting exclusively on peritoneal carcinomatosis of gynaecological, gastric and colorectal origin

Primary cancer	No. of studies	No. of patients	No. of PIPAC procedures	≥ 2 PIPAC procedures (%)	Toxicity grade 3–5 (%)*	Simultaneous treatments (%)	Limitations
Gynaecological	3 ^{44–46}	184	416	38–67	15–28	CRS: 44 ⁴⁴	30% with distant metastases ²⁸
Gastric	2 ^{28,48}	34	82	70–71	20–37	Systemic: 33 ⁴⁸	
Colorectal	1 ⁴⁹	17	42	82	23	Systemic: 65	

Case reports were not included in this analysis. *Common Terminology Criteria for Adverse Events grades. PIPAC, pressurized intraperitoneal aerosol chemotherapy; CRS, cytoreductive surgery.

Table 4 Prospective studies on pressurized intraperitoneal chemotherapy

Trial number	Country	Design	Status	Research question	Primary
NCT02604784	Italy	Single-arm phase II	Recruiting	Feasibility, efficacy and safety of PIPAC	Colorectal, ovarian and gastric cancer, and CUP
NCT02735928	Italy	Single-arm phase II	Recruiting	Feasibility, efficacy and safety of PIPAC	Ovarian cancer
NCT02320448	Denmark	Single-arm phase II	Active, not recruiting	Feasibility and safety of PIPAC	n.a.
NCT01854255	Germany	Single-arm phase II	Completed	Feasibility, efficacy and safety of PIPAC	Gastric cancer
NCT02475772	Germany	Single-arm phase I Dose escalation	Recruiting	Safety and tolerability of doxorubicin and cisplatin every 4 weeks using a three-group, dose-escalation protocol	Ovarian cancer

Prospective clinical trials registered at ClinicalTrials.gov on 12 December 2016. PIPAC, pressurized intraperitoneal aerosol chemotherapy; CUP, cancer with unknown primary; n.a., not available.

0–12 per cent; highest rates were described in a study⁴⁴ that combined PIPAC with CRS, a concept that was abandoned. Postoperative adverse events were assessed by the CTCAE grading system¹² in most studies. Commonly described CTCAE grade 1–2 events were abdominal pain and nausea. CTCAE grades 3–5 were described in 0–37 per cent; highest rates were described in a study⁴⁴ that combined PIPAC with CRS and a study⁴⁸ on gastric peritoneal metastases (Table 3). Two deaths were reported by Naziradze and colleagues⁴⁸ in patients with gastric cancer (1 lung oedema due to ascites removal, 1 disease progression with bowel invasion), and one death from anasarca by Giger-Pabst and colleagues²⁸. A direct causative relationship with PIPAC was considered unlikely. Repeated PIPAC applications (at least 2) were possible in 38–82 per cent. Mean hospital stay was 3 days in the only study⁸ that reported on this outcome.

Toxicity and systemic uptake

Maximal peripheral venous doxorubicin concentrations after PIPAC were 4.0–6.2 ng/ml; half-lives ranged from 86 to 468 min¹⁰. Two studies^{8,42} evaluated renal and hepatic toxicity, and inflammatory response. After PIPAC alone, a transient rise in serum γ -glutamyltransferase level was observed. Other liver parameters and renal tests remained within the normal range, and no cumulative toxicity was noted⁴². Consistent findings were reported for PIPAC in combination with systemic chemotherapy with regard

to absence of hepatorenal toxicity. Leucocytosis and an increase in C-reactive protein level were recorded after most procedures⁸.

Efficacy

The first human application was described in November 2011¹⁰, so long-term follow-up data were not available. The treatment response according to RECIST¹³ was 62–88 per cent in the only phase II trial⁴⁵. In the other studies, histopathological tumour regression was used to evaluate efficacy. An objective tumour response rate of between 62 and 100 per cent was described, but pathological assessment was inconsistent^{52,53} (Table 2). A novel Peritoneal Regression Grading Score was therefore developed to standardize histological assessment²⁹ (Table 2). Median survival after PIPAC was 11–14.1 months for ovarian and gynaecological, 13.4–15.4 months for gastric and 15.7 months for colorectal peritoneal carcinomatosis.

In a recent publication³⁸, changes in gene expression during PIPAC therapy were prognostic of overall survival, suggesting a molecular tumour response in peritoneal cancer.

Quality of life

Five publications^{8,9,45–47} reported on QoL after PIPAC. The German pioneer group⁹ analysed QoL scores on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-30 questionnaire retrospectively in 91 patients, and described no therapy-related

deterioration in QoL, with an absence of gastrointestinal symptoms. An independent Italian group⁸ confirmed these results by assessing QoL with Short Form 36 (SF-36®; Medical Outcome Trust, Health Assessment Laboratories and QualityMetric, Lincoln, Rhode Island, USA) and EORTC QLQ-30 questionnaires in 14 patients having PIPAC in combination with intravenous chemotherapy. The prospective phase II trial of Tempfer and colleagues⁴⁵ demonstrated increasing EORTC QLQ-30 pain scores during PIPAC, with all patients reporting at least some form of abdominal pain. Apart from dyspnoea scores, which increased during treatment, global physical health and gastrointestinal scores improved. The same group reported improved EORTC QLQ-30 scores for global physical health, nausea/vomiting, appetite and constipation under therapy in a retrospective cohort study⁴⁶.

Discussion

Preclinical data suggested improved intraperitoneal distribution and higher tissue concentrations of chemotherapy agents in PIPAC compared with HIPEC. PIPAC appeared to be safe and feasible in most patients. Clinical and histological response rates were around 70 per cent in treated patients with end-stage peritoneal disease of various origins. However, available data are limited by heterogeneity, small sample size and the absence of control groups.

PIPAC is a new technique, and no long-term results are available. Study quality was modest, and no randomized trial has yet been performed. Most studies analysed small cohorts, lacked comparative control groups and were conducted retrospectively. Study heterogeneity was high, but surgical approach and administration of PIPAC were standardized and consistent. Choice of drugs and concentrations of agents used in PIPAC were defined arbitrarily, as were further predefined conditions such as duration of administration, pressure and temperature. Of note, a dose escalation protocol has now been detailed by the pioneer centre (NCT02475772) (Table 4).

Several studies combined different treatments, mainly systemic chemotherapy and PIPAC, but even CRS was performed concomitantly in an earlier study⁴⁴. Hence, observed effects cannot be attributed to PIPAC alone. On the other hand, combined treatments might increase the risk of side-effects or complications, which were still low after PIPAC even when combined with systemic chemotherapy^{8,48,49}. This is important, as concomitant PIPAC and systemic therapy appeared to be well tolerated, also with regard to QoL during treatment^{9,45}. A recent study²⁷ demonstrated a potential role of PIPAC as neoadjuvant therapy before CRS/HIPEC. One of the

most interesting endpoints, efficacy and tumour response, might thus be considerably biased, as it remains unclear which part of the response arises solely from PIPAC. Further, tumour response assessment was not standardized and comparisons were therefore difficult. However, this issue was addressed recently by the development of a novel grading system²⁹.

More recent publications^{37,39–41} were confusing with regard to distribution and penetration of cytostatics. In clinical practice, free distribution is frequently hindered by dense adhesions or extensive peritoneal disease occluding certain areas from detailed exploration, but probably also from intraperitoneal treatment. However, accessibility of aerosolized cytostatics appeared to be superior to that achieved with intraperitoneal chemotherapy by lavage⁷.

Systemic treatment often represents the first-line therapy for peritoneal carcinomatosis and remains the only option in many patients owing to multifocal disease progress beyond the peritoneum. Considerable progress has been achieved with contemporary chemotherapy regimens^{54,55}. However, outcome is worse in patients with stage IV peritoneal carcinomatosis⁵⁶, underlining the need for locoregional treatments. An important drawback of the systemic approach is difficulty in the assessment of tumour response, as the reliability of imaging for diagnostic evaluation of disease progression is modest at best^{57,58}. Therefore, peritoneal carcinomatosis remains undiagnosed in up to 50 per cent of patients⁵⁹ and assessment of treatment response is feasible only either by reoperation or in the presence of a target lesion.

CRS/HIPEC is the only potentially curative option with encouraging results^{6,60,61}. However, because of its considerable morbidity and mortality, this approach is limited to highly selected patients with favourable tumour biology and few co-morbidities. Considering the pharmacokinetic limitations^{4,7} of HIPEC, PIPAC might represent an alternative for patients who are not eligible for radical treatment with curative intent, but whose disease progresses locally in the peritoneum despite systemic treatment. It should be emphasized that encouraging findings regarding feasibility, toxicity and QoL might be explained by the arbitrarily chosen low drug concentrations. Whether the good tolerance of the treatment is due to low systemic uptake alone or because of the low drug doses used in PIPAC remains to be assessed.

To date, no clear indications for PIPAC have been defined. The treatment is probably most effective in milary peritoneal carcinomatosis, because penetration of the drug is better into small nodules than bulky deposits³³. The presence of ascites might facilitate access, and Tempfer and

colleagues⁴⁵ have published data on significant reduction of ascites with repeated applications.

To optimize care, algorithms with predefined indications and contraindications to the available treatment options (systemic chemotherapy, HIPEC and PIPAC) are needed. Further studies should define standardized endpoints to allow better comparison between studies, and comparative groups are mandatory to strengthen the evidence. However, comparative studies in patients with end-stage cancer might represent a methodological and ethical challenge.

Disclosure

The authors declare no conflict of interest.

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