Pressurized Intraperitoneal Aerosol Chemotherapy with Cisplatin and Doxorubicin in Women with Peritoneal Carcinomatosis: A Cohort Study

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Abstract. *Aim: We aimed to assess the objective tumor response (OTR) to laparoscopic pressurized intraperitoneal aerosol chemotherapy (PIPAC) in women with peritoneal carcinomatosis (PC). Patients and Methods: We carried-out a retrospective cohort study of women with PC undergoing repeated courses of PIPAC with 7.5 mg/m^2 of cisplatin and 1.5 mg/m^2 of doxorubicin. OTR was defined as histological regression. Peritoneal carcinomatosis index (PCI) improvement on video-laparoscopy and ascites volume reduction were secondary outcomes. Quality of life was assessed by the European Organization for Research & Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-30+3. Results: A total of 252 PIPACs were performed in 99 women with PC and ovarian (n=84), primary peritoneal (n=6), cervical (n=3), endometrial (n=3), fallopian tube (n=1), and breast (n=1) cancer and pseudomyxoma peritonei (n=1). Laparoscopic non-access rate was 17% (17/99). Fifty women had more than one PIPAC procedures, with an OTR of 76% (38/50) and PCI improvement in 64% (32/50). Ascites volume significantly decreased from 762±1170 ml to 167±456 ml (p=0.02). A high initial Karnofsky Index was correlated with receiving more than one PIPAC (p<0.0001) and a high number of previous surgeries with laparoscopic non-access (p=0.01). Twenty adverse events of Common Terminology Criteria for Adverse Events grade 3 or more were noted. Absence of ascites (odds ratio=8.45, 95% confidence interval=1.9-3.6; p<0.0001), but not patient age, serum cancer antigen-125, and Karnofsky Index independently predicted OTR. EORTC QLQ-30+3 scores for global physical health, nausea/vomiting, appetite loss, and constipation improved during therapy. Conclusion: PIPAC with cisplatin and doxorubicin is an active treatment in women with PC and preserves quality of life. Appropriate patient selection regarding performance status and the number of prior surgeries is important.*

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Peritoneal carcinomatosis (PC) associated with malignancies such as ovarian cancer is difficult to treat. Survival of affected women is poor, with a median duration of overall survival of 10 months (1). During that time, PC significantly compromises the quality of life, with typical and common symptoms such as ascites, abdominal pain, malnutrition, nausea, emesis, and bowel obstruction (2). Paracentesis for ascites relief and systemic chemotherapy with platinum, topotecan, or anthracycline-containing compounds are the mainstay of treatment in women with PC and recurrent gynecological cancer (3). Local/regional treatment strategies such as peritonectomy alone, or combined with hyperthermic intraperitoneal chemoperfusion (HIPEC), have been reported to achieve sustained treatment responses in selected patients with PC and recurrent colonic, gastric, and ovarian cancer (4). However, HIPEC needs careful patient selection and results in considerable morbidity and mortality, with grade 3 and 4 morbidity rates of 23% and 22%, respectively, and a 1-7% mortality rate (4, 5). Clearly, there is an unmet need for effective and well-tolerable additional treatment options for gynecological patients with PC.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new, minimally-invasive drug-delivery technique specifically addressing limited tissue penetration and poor drug distribution, which are the major obstacles to effective

intraperitoneal chemotherapy. PIPAC is based on the assumption that intraabdominal application of chemotherapy under pressure will enhance tumor drug uptake and increase the intra-abdominal area covered by chemotherapy (6-8). PIPAC has been demonstrated to achieve a superior drug distribution on the peritoneum and a better drug penetration into peritoneal nodules compared to conventional intraperitoneal chemotherapy in *ex vivo* and *in vivo* models (9, 10). In the human patient, the tissue concentration of doxorubicin was up to 200-times higher after PIPAC than after HIPEC, in spite of a 90% dose reduction (11). In patients with PC, PIPAC induced regression of peritoneal nodules with minimal hepatic and renal toxicity (12). In addition, the procedure has been shown to be safe regarding occupational health aspects such as air contamination of the operating theatre with aerosol chemotherapy particles (13). In a preliminary series of 18 patients with platinum-resistant recurrent ovarian cancer and PC treated with PIPAC, eight women underwent repeated PIPAC procedures and objective tumor response (OTR) was observed in six of them (14). Cumulative survival after 400 days was 62% and mean actuarial survival time was 442 days. In addition, a recent open-label, single-arm phase II study in 53 patients with recurrent ovarian cancer and PC established the safety and efficacy of three courses every 28-42 days of PIPAC with 1.5 mg/m^2 of doxorubicin followed by 7·5 mg/m^2 of cisplatin (15). Specifically, in that study, 33/53 (62%) patients had an OTR: three had a partial response and 30 patients had stable disease. Tumor regression on histology and PC Index (PCI) improvement were observed in 26/34 (76%) and in 26/34 (76%) patients who underwent all three PIPACs. Typical side-effects of systemic chemotherapy, such as alopecia, peripheral neurotoxicity, nausea and myelosuppression, were not observed. Based on these data, we applied PIPAC with cisplatin and doxorubicin to women with PC from various gynecological malignancies undergoing PIPAC with cisplatin and doxorubicin. The aim of the present cohort study was to assess if the favorable results seen in preliminary studies (14) could be confirmed in a larger cohort of patients.

Patients and Methods

Study design and patients. Between December 2011 and January 2015, 99 women with PC and gynecological malignancies were treated with PIPAC. Institutional Review Board approval for an off-label use program of PIPAC in women with PC was obtained. All women signed an informed consent form. The indication for PIPAC was determined on an individual basis at the Institutional Interdisciplinary Tumor Board. All patients had clinical or radiological evidence of PC with a diagnosis of recurrent gynecological cancer. Patients with extraperitoneal disease were not treated, with the exception of isolated pleural carcinomatosis/effusion, because PIPAC was not expected to affect extra-abdominal disease. Patients with a history of allergic reactions to platinum compounds or doxorubicin were not accepted for PIPAC.

PIPAC procedure. A minimum delay of four weeks between PIPAC and the last application of systemic chemotherapy was observed. The PIPAC procedure was performed as described previously (11). Briefly, after insufflation of a 12 mmHg CO_2 pneumoperitoneum, two balloon safety trocars (5 and 12 mm; Applied Medical, Düsseldorf, Germany) were inserted into the abdominal wall in an operating room equipped with laminar airflow. Video documentation was started and the PCI was determined according to Sugarbaker, based on lesion size and distribution (16). 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 PC grade ranging from 0-3, *i.e.* no visible carcinomatosis, isolated tumor nodules, multiple tumor nodules, and confluent lesions, respectively. The sum of grades for all 13 points was recorded as the PCI. A biopsy was taken for histological confirmation of PC during the first procedure and all subsequent procedures in order to ascertain tumor regression. Ascites volume was documented and ascites was removed.

A nebulizer (MIP®, Capnomed, Villigendorf, Germany) was then connected to an intravenous high-pressure injector (Mark7®; Arterion, Medrad, Leverkusen, Germany) and inserted into the abdomen. The tightness of the abdomen was documented *via* zero flow of CO_2. A pressurized aerosol containing cisplatin at a dose of 7.5 mg/m^2 body surface in 150 ml of 0.9% NaCl solution followed by doxorubicin at a dose of 1.5 mg/m^2 body surface in 50 ml of 0.9% NaCl solution were applied *via* nebulizer and injector. The dosage used in this cohort study was based on previous clinical experience in patients with peritoneal carcinomatosis treated with PIPAC at this dosage and in this formulation (13, 14). Safety measures for PIPAC have been described elsewhere (13). Briefly, a 3-level confinement system was implemented, consisting of the tightly closed abdomen, the laminar air flow, and of the operating room itself, since the procedure is remote-controlled. The pressurized chemotherapy aerosol was maintained for 30 min at a temperature of 37˚C. The chemotherapy aerosol was then scavenged *via* a closed line over two sequential microparticle filters and vented into the airwaste system of the hospital in such a manner that occupational re-exposure did not occur. Finally, trocars were retracted and laparoscopy ended. No drainage of the abdomen was applied. The PIPAC procedure was repeated after 4-6 weeks until progression or limiting toxicity.

Efficacy and safety assessment. Histological regression was assessed by the Department of Pathology, Bergmannsheil Hospital, Ruhr University Bochum, Bochum, Germany, by grading tumor biopsies taken during each PIPAC. Histopathological tumor regression was graded as follows: vital tumor cells, mild regression, strong regression, and no tumor cells, as previously described (17).

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (18). Quality of life was measured by the European Organization for Research & Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30+3, a validated tool for assessing quality of life in patients with cancer (19). Some patients underwent cytoreductive surgery (CRS) followed by PIPAC immediately after CRS or within 10 days thereafter. Criteria for CRS were a good performance status (Karnofsky Index >80%), optimal/complete cytoreduction at initial debulking surgery, and lesions which were deemed resectable based on computed tomographic scan (20).

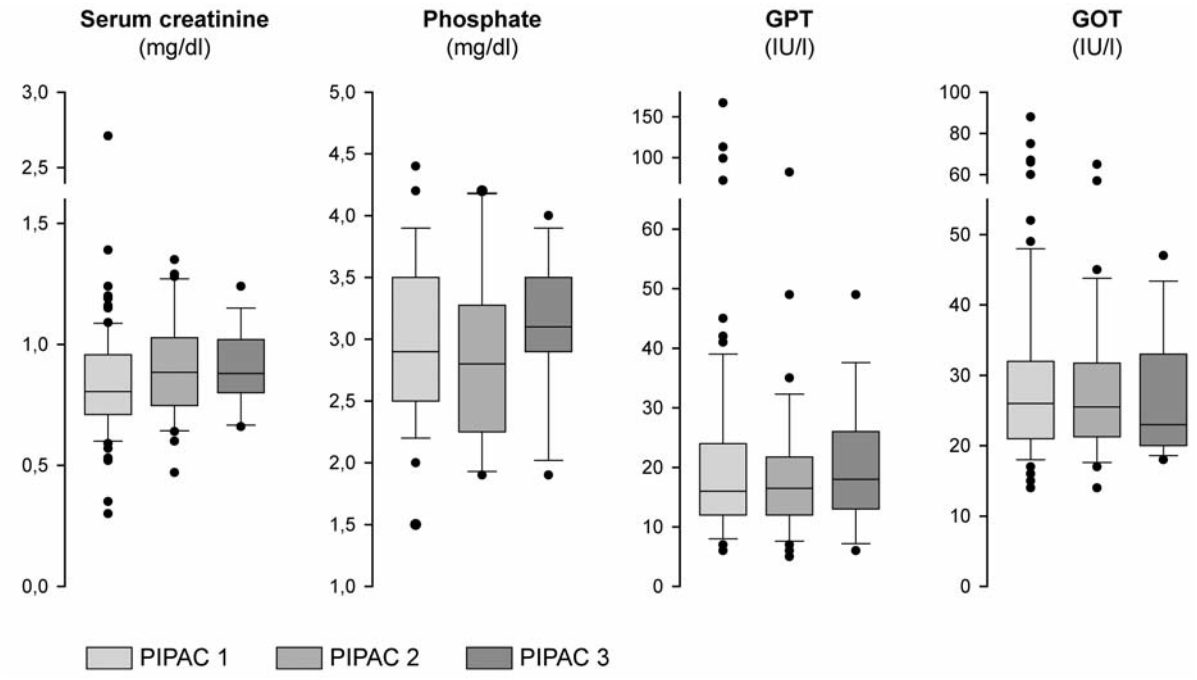

Figure 1. *Box plots of creatinine, phosphate and liver transaminases glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) during pressurized intraperitoneal aerosol chemotherapy (PIPAC) cycles 1 to 3. Boxes represent the median and the upper and lower quartiles, whiskers indicate the 10th and 90th percentiles, outliers are shown as dots.*

Statistics. All *p*-values are two-tailed and a *p*-value of less than 0.05 was considered statistically significant. Values are given as means or medians, where appropriate. We performed a multivariable logistic regression model with OTR (yes *vs*. no) as the dependent variable and patient age (<70 *vs*. ≥70 years), serum cancer antigen-125 (CA-125) (<1000 *vs*. >1000 U/ml), Karnofsky Index (<80% *vs*. >80%), and the presence of ascites (yes *vs*. no) as independent variables. Survival was modelled in a Kaplan–Meier survival curve. We used SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA) and SigmaPlot 12 (Systat Software Inc., San José, CA, USA) for statistical analyses.

Results

Patients. A total of 252 PIPAC procedures were performed in 99 women with PC and ovarian cancer (n=84), fallopian tube cancer (n=1), primary peritoneal cancer (n=6), pseudomyxoma peritonei (n=1), cervical cancer (n=3), endometrial cancer (n=3), and breast cancer (n=1). The mean age of this cohort was 60±12 years. Ascites and pleural effusion were present in 45 and 10 patients, respectively. Patients' characteristics including the number of previous chemotherapy lines are shown in Table I. Laparoscopic non-access rate was 17% (17/99). Thus, 82 women underwent at least one PIPAC procedure and were eligible for safety analysis. Fifty women underwent more than one PIPAC and were eligible for efficacy analysis. Specifically, 49, 16, 22, 4, and 8 women underwent one, two, three, four, and more than four PIPACs, respectively. The median number of PIPACs administered was 2.2 (minimum one, maximum eight).

Table I. *Characteristics of 99 women with recurrent, platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer undergoing pressurized intraperitoneal aerosol chemotherapy.*

Characteristic	Value
Number of patients	99
Age (mean±SD), years	60±12
Karnofsky Index, median (range)	70 (40-100)
Number of prior chemotherapy regimens (mean±SD)	2.4±1.6
Adjuvant radiotherapy	None
Presence of pleural effusions	10/99 (10%)
Presence of ascites	45/99 (45%)
PCI (mean±SD)	16.6±10.3
Serum CA125 (U/ml; mean±SD)	2041±4329

SD: Standard deviation; PCI: Peritoneal Cancer Index.

Safety and efficacy. Among 50 women with more than one PIPAC, tumor regression on histology was noted in 76% (38/50) and PCI improvement on repeated video-laparoscopy was noted in 64% (32/50). Median ascites volume decreased significantly

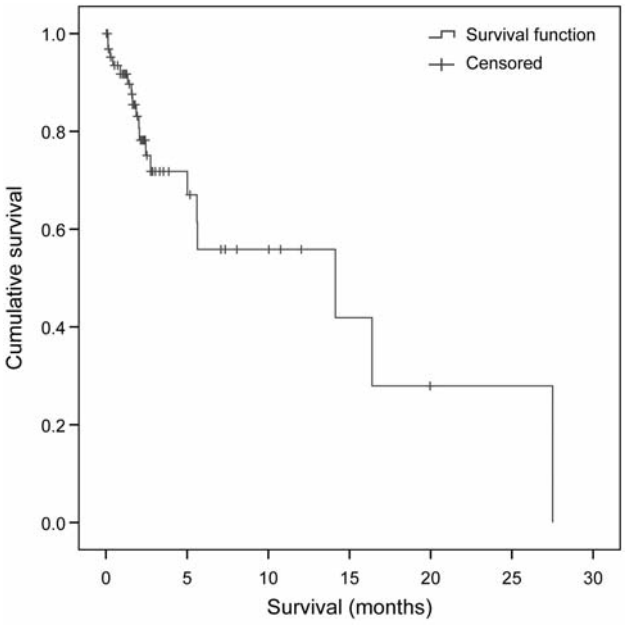

Figure 2. *Kaplan–Meier survival curve of 82 women who had undergone at least one pressurized intraperitoneal aerosol chemotherapy treatment.*

Table II. *Adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) in 99 patients undergoing pressurized intraperitoneal aerosol chemotherapy (PIPAC).*

	CTCAE, n (%)			
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Trocar hernia	-	1 (1%)	-	-
Abdominal pain	55 (56%)	44 (44%)	-	-
Bowel obstruction	1 (1%)	1 (1%)	1 (1%)	-
Small bowel perforation*	-	-	1 (1%)	-
Small bowel fistula	-	-	-	1 (1%)
Colon perforation*	-	-	1 (1%)	1 (1%)
Anemia	1 (1%)	8 (8%)	4 (4%)	-
Sepsis	-	-	2 (2%)	-
Vomiting	-	1 (1%)	-	-
Infection	-	4 (4%)	-	-
Trocar metastasis*	-	-	1 (1%)	-
Breast cancer	-	-	1 (1%)	-
Bowel anastomosis insufficiency*	-	-	-	1 (1%)
Hypertension	-	-	1 (1%)	-
Bile duct stenosis		-	1 (1%)	-
Hypocalcemia		1 (1%)	-	-
Respiratory insufficiency		-	4 (4%)	-
Fever	10 (10%)			

*After PIPAC combined with cytoreductive surgery.

during therapy from 762±1170 ml to 167±456 (p=0.02). Figure 1 shows box plots of serum creatinine, phosphate, and liver transaminases glutamic oxaloacetic transaminase (GOT) and gamma glutamic transaminase (GGT) during PIPAC courses 1 to 3, as measures of cumulative renal and liver toxicity.

A good initial Karnofsky Index was correlated with receiving more than one PIPAC course (Spearman correlation coefficient=0.463; p<0.0001). A high number of previous surgeries was correlated with laparoscopic non-access (Spearman correlation coefficient=0.264; p=0.01). In a multivariable regression analysis with OTR as the dependent variable, absence of ascites [odds ratio (OR)=8.45; 95% confidence interval (CI)=1.9-3.6; p<0.0001], but not patient age (OR=0.79, 95% CI=0.2-4.2; p=0.7), serum CA-125 (OR=0.34, 95% CI=0.1-1.9; p=0.2), or Karnofsky Index (OR=4.05, 95% CI=0.9-17.1; p=0.6) independently predicted OTR.

The median actuarial survival time of patients overall was 14.1 months after the first PIPAC. Cumulative survival after 12 and 24 months was 56% and 28%, respectively. A total of 24 patients died due to disease progression during follow-up. All deaths were judged to be due to disease progression. The median duration of follow-up was 126 (±164) days. Figure 2 shows a Kaplan–Meier survival curve of all patients who had undergone at least one PIPAC course.

CTCAE grade 1 to 4 toxicities were observed in 57, 60, 17 and three patients, respectively; there were no grade 5. Table II describes the observed toxicities in detail. For example, most patients (55/99) had mild abdominal pain after PIPAC. Of note, five surgical complications CTCAE grade 3/4 (small bowel perforation, colon perforation, bowel anastomosis insufficiency, trocar metastasis) occurred in women who had both CRS and PIPAC. No perioperative or in-house mortality occurred.

Quality of life. Quality of life was measured using the EORTC QLQ-30+3 questionnaire one day before every PIPAC course. A total of 58, 31, 22, 9, 6, 4, 2, and 1 patient filled in the questionnaires at time points PIPAC 1-8, respectively. Global physical health scores improved during therapy. Specifically, global physical health scores (revised) were 47.1 (95% CI=40.2 to 53.9), 62.4 (95% CI=52.8 to 72.0), 53.0 (95% CI=40.5 to 65.6), 52.8 (95% CI=34.4 to 71.2), 66.7 (95% CI=41.3 to 92.0), and 60.4 (95% CI=18.0 to 102.9) at time points PIPAC 1 to 6, respectively. Figure 3 shows the quality of life data in detail. In addition to the improvement of global physical health scores, symptom scores for nausea/vomiting, appetite loss, pain, and constipation also improved during therapy, demonstrating that PIPAC does not increase gastrointestinal toxicity. However, diarrhea, insomnia, and dyspnea scores increased during therapy. Scores for physical, role, emotional, and social functioning demonstrated a continuous improvement during therapy. Cognitive functioning improved during the first four PIPACs and declined thereafter (Figure 3).

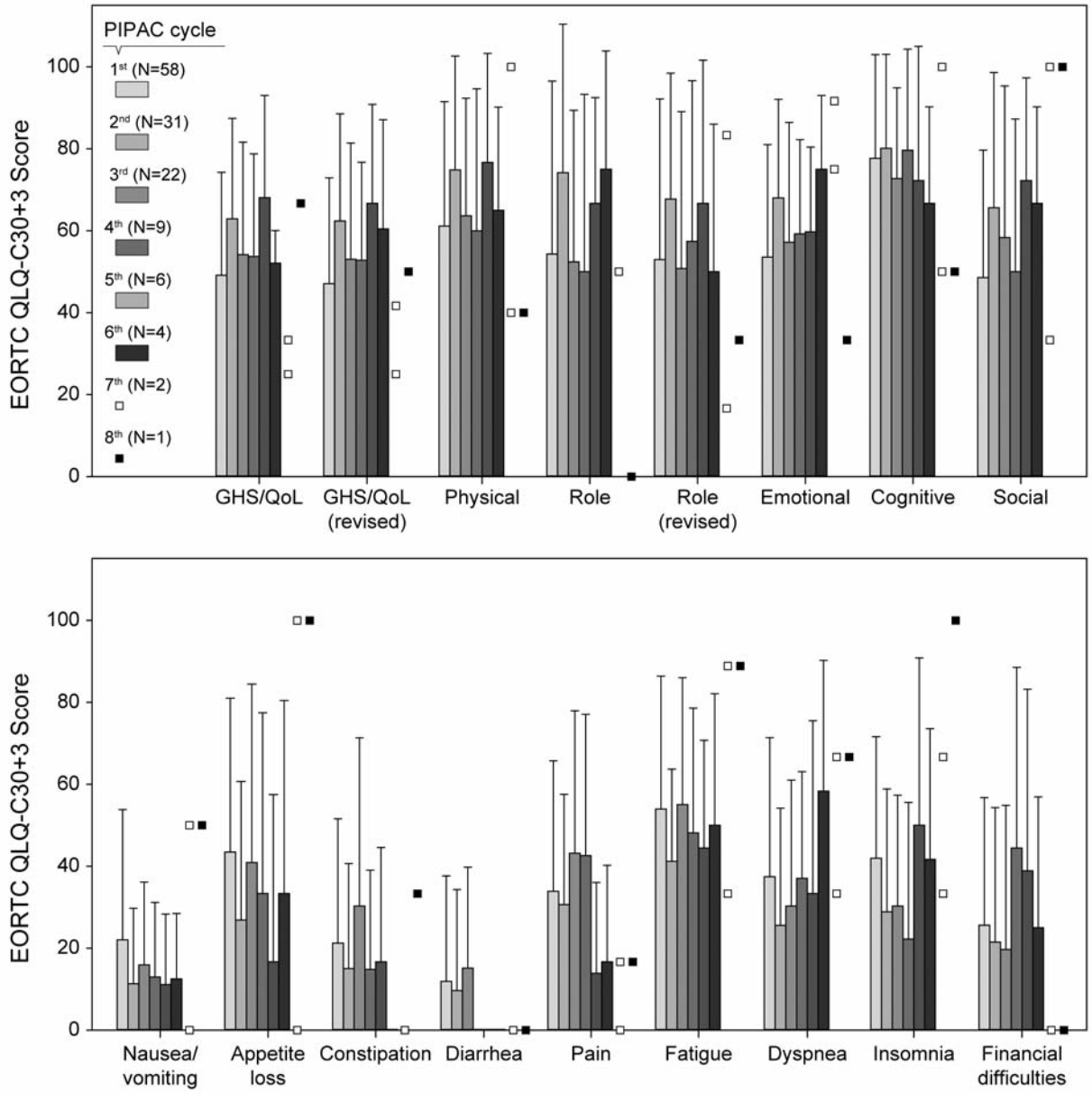

Figure 3. *Quality of life scores according to the European Organization for Research and Treament of Cancer Quality of Life Questionnaire (EORTC QLQ-C30+3) during pressurized intraperiotneal aerosol chemotherapy (PIPAC) treatment cycles 1 to 8 are shown (number of patients are indicated). Bars represent means, whiskers the 95% confidence interval of the means (cycles 1-6), boxes represent individual data points (at cycles 7 and 8, with N=2 and N=1, respectively).*

Discussion

In this retrospective series of 252 PIPAC procedures in 99 women with PC, repeated PIPAC was active and achieved an OTR in 76% of women. Median ascites volume significantly decreased during therapy and PCI improved in 64% of patients. Quality of life measured by the EORTC QLQ-30+3 questionnaire demonstrated improvement of global physical health, nausea/vomiting, appetite loss, constipation, physical, role, emotional, and social functioning scores during PIPAC. There was no cumulative renal or hepatic toxicity and, overall survival after 12 months was 56%. These data confirm results of a preliminary study (14) and suggest that PIPAC may be a new palliative treatment option for selected patients with PC. Based on these results, PIPAC may be further investigated in comparative clinical trials.

The data reported in this cohort of women with PC are in accordance with previous reports describing clinical activity

of PIPAC in patients with PC from both gynecological and non-gynecological cancer such as pseudomyxoma peritonei, colon, and appendiceal cancer (11-15, 21). Currently, PIPAC is being tested in a clinical phase II trial in patients with gastric cancer based on favorable preliminary clinical experience (22). Together, these data suggest that PIPAC may be a therapeutic option for PC from various origins of cancer.

In the present study, we analyzed a heavily pre-treated population of women with a mean of 2.4 previous lines of chemotherapy. Therefore, it can be assumed that most tumors in this patient population were platinum-resistant. PIPAC has the potential to overcome chemotherapy resistance by delivering chemotherapy locally and under pressurized conditions. In this way, PIPAC achieves high peritoneal concentrations of the chemotherapeutic compounds applied (9, 11). One methodological advantage of PIPAC compared to systemic chemotherapy is that the antitumor effect can be directly measured in tumor biopsies taken during each PIPAC. Using regression grading of repeated tumor biopsies taken during sequential PIPAC cycles, we determined an OTR of 76% in this patient population. This provides evidence of a direct antitumor effect and indicates that PIPAC is able to overcome platinum resistance in at least some PC tumor cells.

Treatment toxicity was measured using CTCAE criteria. We found that PIPAC was safe and had a manageable toxicity profile. CTCAE grade 3 and 4 toxicities were observed in 17% and 3%, respectively and there was no grade 5 event. However, most patients had transient abdominal pain or fever after PIPAC which is consistent with a local chemical peritonitis induced by PIPAC. Of note, five surgical complications of CTCAE grade 3 or 4 (small bowel perforation, two colon perforations, bowel anastomosis insufficiency, trocar metastasis) occurred in women who had both CRS and PIPAC. As expected, combining CRS and PIPAC increases surgery-related morbidity and is therefore not recommended.

All patients in this study were in a palliative situation. Therefore, it is important to assess the effect of any antitumor therapy on the quality of life. Specifically, we measured the quality of life during PIPAC using a validated tool, the EORTC-QLQ 30+3 questionnaire. Confirming preliminary evidence from a phase II clinical trial (15), we found that PIPAC induced a sustained improvement of overall global physical health. Specifically, global physical health scores improved from 47.1 at PIPAC 1 to 62.4, 53.0, 52.8, 66.7, and 60.4 at time points PIPAC 2 to 6, respectively. Thus, global quality of life improved after the first therapy and remained so during all subsequent treatment cycles. In addition to the improvement of global physical health, symptom scores for nausea/vomiting, appetite loss, pain, and constipation also improved during therapy, demonstrating that PIPAC does not increase gastrointestinal toxicity. Scores for physical, role, emotional, and social functioning demonstrated a continuous improvement during therapy.

The stabilization of quality of life under PIPAC therapy appears encouraging considering the limited life expectancy of the patients treated in this study. This effect was only observed in women able to receive repeated PIPACs. Thus, a selection bias cannot be excluded. However, this bias is not specific to this cohort of patients but is a common methodological problem in assessing quality of life in end-stage patients, since many patients will not be able to receive the therapy scheduled over a longer period of time. Specifically, our data confirm that low-dose PIPAC with cisplatin and doxorubicin does not induce significant gastrointestinal symptoms or complications, an observation consistent with the results of a phase II trial assessing safety and efficacy of PIPAC with doxorubicin and cisplatin (15).

In the present study, a good initial performance status correlated with receiving more than one PIPAC and a high number of previous surgeries was significantly correlated with laparoscopic non-access. These are findings valuable for optimizing patient selection prior to PIPAC. Women with a limited number of previous abdominal surgeries are thus not optimal candidates for PIPAC. The high laparoscopic non-access rate of 17% associated with PIPAC might be reduced by limiting this procedure to women with a minimum of previous surgeries.

Conclusion

PIPAC is an effective treatment in women with PC. Intra-abdominal application of pressurized chemotherapy as an aerosol should be further investigated in comparative clinical trials in this patient population.

Conflicts of Interest

M. Reymond discloses that he is holding a patent for the high-pressure device used to deliver the intraperitoneal chemotherapy described in this article, and that he has received royalties from Reger Medizintechnik GmbH, Rottweil, Germany. The other Authors have no conflicts of interest.

Acknowledgements

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