Gynecologic Oncology 137 (2015) 223–228

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study

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HIGHLIGHTS

- Pressurized intraperitoneal aerosol chemotherapy (PIPAC) was studied in women with recurrent ovarian cancer.
- Tumour regression on histology was observed in 26/34 (76%).
- Quality of life including physical health, nausea/vomiting, appetite loss, diarrhea, and constipation improved during therapy.

ARTICLE INFO

Article history:
Received 19 January 2015
Accepted 11 February 2015
Available online 18 February 2015

Keywords:
Recurrent ovarian cancer
Platinum-resistant
Chemotherapy
Intraabdominal
High pressure

ABSTRACT

Objective. Recurrent ovarian, fallopian or peritoneal cancer with peritoneal carcinomatosis (ROCPC) is resistant to systemic chemotherapy. We assessed the safety and activity of laparoscopic pressurized intraperitoneal aerosol chemotherapy (PIPAC) in women with this cancer.

Methods. In this open-label, single-arm phase 2 study, patients underwent 3 courses q 28–42 days of PIPAC with doxorubicin 1 · 5 mg/m^2 followed by cisplatin 7 · 5 mg/m^2. A pressure of 12 mm Hg and a temperature of 37 °C were applied for 30 min/course. The primary endpoint was the proportion of patients who had an objective tumor response (OTR) according to RECIST version 1.1 criteria. Analysis was by intention to treat. Secondary endpoints were tumor regression on histology, PC Index improvement on repeated video-laparoscopy, and quality of life measured with the EORTC QLQ-30 questionnaire.

Results. Sixty-four patients were enrolled. Laparoscopic non-access rate was 11/64 (17%). 53 patients were eligible for analyses. 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 improvement were observed in 26/34 (76%) and in 26/34 (76%) patients who underwent all 3 PIPACs. There were no treatment-related deaths. No grade 4 toxicity was observed. Grade 3 toxicities were trocar hernia (n = 2), bowel obstruction (n = 2), abdominal pain (n = 2), hematoma (n = 1), intraoperative bleeding (n = 1), and cystitis with urosepsis (n = 1). EORTC QLQ-30 global physical health scores, nausea/vomiting, appetite loss, diarrhea, and constipation improved during therapy.

Conclusion. PIPAC is well tolerated and active in women with ROCPC and warrants further investigation in these patients.

Introduction

Ovarian cancer is a rare disease with a life-time risk of 1 · 7% [1]. It is, however, the most lethal of all pelvic malignancies with recurrence rates of 60–85% within five years after primary treatment [1, 2]. Recurrent ovarian cancer is difficult to treat and intravenous chemotherapy with platinum compounds, taxanes, anthracyclines, gemcitabine, topotecan, and trabectedin in various combinations and sequences are typically used. These regimens achieve median overall survival rates after the first, second, third, fourth, and fifth relapses of 17.6 (95% CI 16.4–18.6), 11.3 (10.4–12.9), 8.9 (7.8–9.9), 6.2 (5.1–7.7) and 5.0 (3.8–10.4) months, respectively [2].

Intraperitoneal chemotherapy (IPC) in patients with recurrent ovarian cancer is an experimental approach limited by poor drug distribution and tumor penetrance [3–6]. One potential way to overcome the

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http://dx.doi.org/10.1016/j.ygyno.2015.02.009
0090-8258/

pharmacokinetic limitations of IPC is to apply chemotherapy as a pressurized aerosol in order to take advantage of the physical properties of gas and pressure [1]. This approach is based on the assumption that intraabdominal application of chemotherapy under pressure will enhance tumor drug distribution and uptake [7–9]. In an animal model using five pigs PIPAC had a better distribution of a pressurized test dye within the abdominal cavity and a better penetration into the peritoneum compared to peritoneal lavage [10]. In addition, improved drug penetration was suggested in an ex vivo study using a fluorescence-marked non-toxic therapeutic agent (Dbait) [11].

Based on these experimental data, pressurized intraperitoneal aerosol chemotherapy (PIPAC) with doxorubicin and cisplatin was applied to three end-stage patients with recurrent peritoneal carcinomatosis (PC) [12]. In these preliminary applications, PIPAC resulted in high local tumor concentrations of doxorubicin (4.1 μmol/g) and induced regression of peritoneal nodules with limited hepatic and renal toxicity. In a case series of 18 patients with recurrent ovarian cancer and PC, PIPAC led to an objective tumor response in six patients with an acceptable toxicity [13]. In addition, PIPAC has been shown to be safe regarding occupational health aspects such as operation theater air contamination with aerosol chemotherapy particles [14].

Based on this preliminary information, we tested PIPAC with cisplatin and doxorubicin in patients with recurrent, platinum-resistant ovarian, fallopian, or peritoneal cancer and PC (ROCPC) in a phase 2 trial.

Materials and methods

Women with ROCPC after at least two lines of standard systemic chemotherapy were eligible for enrolment in this open-label, single-arm, phase 2 study. Specifically, women with 'platinum-sensitive' recurrence, i.e. recurrence >6 months after completion of the adjuvant chemotherapy, were required to have undergone at least two chemotherapy lines in addition to the adjuvant regimen. Women with 'platinum-resistant' recurrence, i.e. recurrence within 6 months after completion of the adjuvant chemotherapy, were required to have undergone at least one chemotherapy line in addition to the adjuvant regimen. Lastly, women with 'platinum-refractory' recurrence, i.e. recurrence during the adjuvant chemotherapy, were required to have undergone at least one chemotherapy line in addition to the adjuvant regimen. Using these criteria, all women entering the study had a platinum-resistant tumor at the time of study entry. Institutional review board approval for this study was obtained (Ethics Committee of the Ruhr University Bochum, Bochum, Germany; registry number 4515-12 FF; issue date Jan 28, 2013). This study was approved by the German national drug safety agency (BfArM; registry number 61-3910-4039261). This study was registered with ClinicalTrials.gov, number NCT01809379, and EudraCT, number 2012-004397-26. All women signed an informed consent form. Women were eligible, if they had clinical and/or radiological evidence of PC; an age between 18 and 85 years; a good performance status (Karnofsky Index > 70%), a diagnosis of recurrent disease with disease progression; blood, electrolyte counts, liver, and renal function parameters within 10% of the normal range established in the laboratory of the study institution; had provided written informed consent, and were postmenopausal or ovariectomized. Women were ineligible, if they had extraabdominal metastatic disease including retroperitoneal disease such as aortic/paraaortic lymph node recurrence with the exception of isolated pleural carcinomatosis/effusion; had underwent chemotherapy or surgery within the last four weeks prior to study enrolment or a previous treatment with the maximum cumulative dose of doxorubicin, daunorubicin, epirubicin, idarubicin, and/or other anthracyclines and anthracenediones; had a history of allergic reactions to cisplatin or other platinum containing compounds or doxorubicin; had severe renal impairment or severe hepatic impairment with organ-specific functional parameters >twice the upper norm; had a history of myocardial insufficiency not controlled by concurrent medication, severe cardiac arrhythmia not controlled by concurrent medication, or recent myocardial infarction or myelosuppression; had an immunocompromised status such as immunosuppressive therapy or a known disease of the immune system; were previously enrolled in the present study; and had underwent any form of previous intraabdominal chemotherapy or intraabdominal antibody therapy. Also, women were not allowed to undergo any cancer-specific treatment during the trial. Secondary debulking surgery was not allowed during PIPAC treatment.

The PIPAC procedure was performed as follows: after insufflation of a 12 mm Hg CO_2 pneumoperitoneum, two balloon safety trocars (5 and 12 mm, Applied Medical, Duesseldorf, Germany) were inserted into the abdominal wall in an operating room equipped with laminar airflow. Video documentation was started and the PC Index (PCI) was determined according to Sugarbaker, based on lesion size and distribution [15]. Using a pictorial of the abdomen, each location of a 13 point list (central abdominal wall, epigastrium, right lower abdominal wall, right upper abdominal wall, right flank, left lower abdominal wall, left upper abdominal wall, left flank, pelvis, upper jejunum, lower jejunum, upper ileum, lower ileum) received a peritoneal carcinomatosis grade ranging from 0 to 3, i.e. no visible carcinomatosis, isolated tumor nodules, multiple tumor nodules, and confluent lesions. The sum of all 13 grades was noted as PCI. A biopsy was taken for histologic confirmation of PC during the first procedure and all following procedures in order to ascertain tumor regression. Ascites volume was documented and ascites was removed. Then, a nebulizer (Reger Medizintechnik, Rottweil, Germany) was connected to an intravenous high-pressure injector (Mark 7 Arterion®, Medrad, Germany) and inserted into the abdomen. The tightness of the abdomen was documented via a zero-flow of CO_2. A pressurized aerosol containing cisplatin at a dose of $7 \cdot 5$ mg/m^2 body surface in a 150 ml NaCl 0.9% solution followed by doxorubicin at a dose of $1 \cdot 5$ mg/m^2 body surface in a 50 ml NaCl 0.9% solution were applied via a nebulizer and an injector. The dosage used in this cohort study was based on previous clinical experience in patients with peritoneal carcinomatosis treated with PIPAC in this dosage and formulation [12,13]. Injection parameters were set at a flow rate of 30 ml/min and a maximum upstream pressure of 200 psi in the high-pressure injector. The injection was remote-controlled to minimize personnel exposure. After application of both drugs, the therapeutic capnoperitoneum was maintained for 30 min at a temperature of 37 °C. Then, the chemotherapy aerosol was exsufflated via a closed line over two sequential microparticle filters into the airwaste system of the hospital. Finally, trocars were retracted and laparoscopy ended. No drainage of the abdomen was applied. The PIPAC procedure was repeated three times every 4–6 weeks. Concomitant cytoreductive surgery was not allowed per protocol.

The primary endpoint of the study, objective tumor response (OTR), was measured according to RECIST criteria, version 1.1 at the end of treatment cycle 3 [16]. Peritoneal, sub-peritoneal, visceral, and pleural manifestations were assessed separately. CT scans were assessed by the Radiology Department, Ruhr University Bochum, Marienhospital Herne. In addition, patients of the per-protocol (PP) population were asked to present for a follow-up CT scan 3 months after completion of 3 PIPAC cycles. CT scans of these patients were then collected, anonymized, and scored by a board-certified radiologist (GW), blinded to previous CT results and all clinical data. Histologic regression was assessed by the Department of Pathology, Ruhr University Bochum, Klinikum Bergmannsheil. In addition, all slides were collected, anonymized, and scored by a board-certified gyneco-pathologist (RH), blinded to the previous histological diagnoses and all clinical data. 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]. In addition, we measured C-reactive protein (CRP) and creatinine in the serum on the day before, the first day after, and the third day after each cycle of