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Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) for Peritoneal Metastases in Solid Organ Graft Recipients: First Experience

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Therapy of peritoneal metastases (PM) in solid organ transplant recipients is challenging. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) might constitute a new therapeutic opportunity for these patients.

Material/Methods: This was a single-center, retrospective analysis of prospective registry data (NCT03210298) in a tertiary care center between 1.7.2016 and 31.12.2017. Intraperitoneal administration of oxaliplatin 92 mg/m^2 body surface or a combination of cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2, repeated every 6 weeks. Objective tumor response was documented via histology (Peritoneal Regression Grading Score, PRGS), adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0.

Results: Out of 71 consecutive patients treated with PIPAC, 2 patients (2.8%) were solid organ transplant recipients. The first patient had metachronous PM of colonic cancer origin after liver transplantation. The second patient had synchronous PM of pancreatic cancer origin after combined kidney-pancreas transplantation. After repeated combined systemic and PIPAC chemotherapy, objective histological response was documented in both patients. No adverse events >CTCAE 2 were recorded. There was no measurable liver or renal toxicity. PIPAC procedures could be repeated (2, resp. 3 cycles) without any interruption of immunosuppressive medication or impairment of respective plasmatic drug levels. The first patient passed away 7 months after the first PIPAC, the second patient was still alive after 8 months.

Conclusions: PIPAC can induce objective regression of PM in solid organ transplant recipients without inducing organ toxicity or interfering with immunosuppressive therapy.

MeSH Keywords: **Antineoplastic Agents • Organ Transplantation • Peritoneal Neoplasms**

Abbreviations: **5-FU** – 5-fluorouracil; **BSA** – body surface area; **CRS** – cytoreductive surgery; **CTCAE** – Common Terminology Criteria for Adverse Events; **HIPEC** – hyperthermic intraperitoneal chemotherapy; **KI** – Karnofsky Index; **OX** – oxaliplatin; **PCI** – peritoneal cancer index; **PIPAC** – pressurized intraperitoneal aerosol chemotherapy; **PM** – peritoneal metastases; **PRGS** – peritoneal regression grading score

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Background

Use of modern immunosuppressive agents has allowed to reduce acute rejection incidence and to prolong graft survival in solid organ transplant recipients. However, the comorbidities caused by immunosuppression remain an ongoing challenge [1]. A particular problem is the increased risk of developing secondary malignancies after solid organ transplantation [2], with a reported prevalence between 4% and 18% or an average incidence of 6% [3].

Peritoneal metastases (PM) can develop after solid organ transplantation. Treatment choices for PM include systemic therapy and, in selected cases, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) [4].

CRS and CRS with HIPEC has been reported for treating PM in curative intent in a single case after liver transplantation [5]. However, in most cases, therapy of PM remains palliative. Antineoplastic drugs have a narrow therapeutic index and the drug dose necessary to induce tumor regression is usually associated with significant hematopoietic, liver, renal, and cardiac toxicity. This is a particular problem in solid organ recipients. Not only solid organ recipients have an increased risk of developing *de novo* neoplasms, but cancer patients often exhibit excretory reduced organ function and are particularly vulnerable to development of renal abnormalities [6]. Chemotherapy can cause liver injury owing to toxic effects or idiosyncratic reactions. Thus, there is a need for optimizing pharmacokinetics and pharmacodynamics of chemotherapeutic drugs in order to improve their tolerance in organ transplant recipients [6].

Against this framework, Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) might represent a new opportunity in this particular clinical situation. PIPAC is applied via video-laparoscopy and delivers chemotherapy into the abdominal cavity as a pressurized normothermic aerosol, which allows a dose reduction by a factor 5 to 20, while increasing at the same time drug concentration in the target tissue by 2 orders of magnitude as compared to liquid/non-aerosolic chemotherapy [7]. Acute and cumulative hepatic and renal toxicities after repeated PIPAC application were found to be minimal [8,9].

We herein present the medical history of 2 patients with PM after orthotopic liver transplantation or combined kidney-pancreas transplantation treated with PIPAC.

Material and Methods

Study design

Single-center, retrospective analysis of prospective registry data in a tertiary care center between July 1, 2016 and December 31, 2017.

Ethical and regulatory background

Patient provided written informed consent for therapy and for data collection. Pseudo-anonymized data were entered into the prospective international PIPAC registry (NCT03210298) hosted by the An-Institute for Quality Control in the Operative Medicine at the University of Magdeburg, Germany. This registry was approved by the Ethics Committee of Ruhr-University Bochum and by the data protection officer of the State of Northrhine-Westfalia in January 2016. When the patients were no candidates for any recruiting oncological study, PIPAC therapy was applied as an off-label procedure.

Therapy

Intraperitoneal administration of oxaliplatin 92 mg/m^2 body surface (patient case 1) or a combination of cisplatin 7.5 mg/m^2 and doxorubicin 1.5 mg/m^2 (patient case 2), repeated every 6 weeks. All interventions were performed under general anesthesia.

Technique

The procedure was performed in an operating room equipped with advanced air filtering systems. PIPAC technique has been described elsewhere [10]. Shortly, after insufflation of a 12 mmHg capnoperitoneum, 2 trocars (5 mm and 12 mm, Kii®, Applied Medical, Düsseldorf, Germany) were inserted into the abdominal wall. Extent of PM was determined. Peritoneal biopsies were taken in all 4 quadrants. A nebulizer (Capnopen®, Capnomed GmbH, Villingendorf, Germany) was connected to an intravenous high-pressure injector (Accutron HP®, MedTron AG, Saarbrücken, Germany) and inserted into the abdomen. The pressurized aerosol containing the chemotherapeutic drugs was applied. Injection was remote-controlled, and no other person remained in the room during application. The therapeutic aerosol was maintained at 12 mmHg for 30 minute at 37°C. Then, it was released safely via a Closed Aerosol Waste System (CAWS). Trocars were retracted, and laparoscopy ended. No drainage was applied.

Safety

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE 4.0). Surgical

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complications were graded according to Dindo-Clavien classification.

Efficacy

Histological tumor response was assessed by an independent anatomopathologist. Objective tumor response was documented via Peritoneal Regression Grading Score, PRGS [11]. PRGS is a 4-tied regression grading system ranging from 4 (vital tumor with no sign of regression) to 1 (complete regression, no tumor cells identified).

Follow-up

Follow-up was obtained by telephone calls until March 27, 2018 or until death.

Statistical analysis

All data were documented according to our institutional rules, including electronic archiving and photographic documentation of the procedures. Data were entered prospectively into the PIPAC registry. Analysis was retrospective. We used Microsoft Excel 2016 (Microsoft Corporation) for analysis and graphical design.

Results

Out of 71 consecutive patients treated with PIPAC, only 2 patients (2.8%) were solid organ transplant recipients. The first patient, a 50-year-old male, suffered from metachronous PM of colonic origin after liver transplantation. The second patient, a 56-year-old male, suffered from synchronous PM of pancreatic origin after combined kidney-pancreas transplantation.

Patient case 1

Orthotopic liver transplantation was performed in 2005 due to primary sclerosing cholangitis. Immunosuppression was maintained with tacrolimus and everolimus. In 2013, a nodal positive adenocarcinoma (UICC stage IIIc) of the right colon was diagnosed and a hemicolectomy performed. The patient received adjuvant chemotherapy with 5-fluorouracil (5-FU) and folinic acid. In December 2016, follow-up contrast-enhanced CT scan showed metachronous PM in the absence of extraperitoneal metastatic sites. After MTB presentation, a palliative combination chemotherapy with 5-FU and bevacizumab (Avastin®) was initiated and interrupted because of toxic side effects. In January 2017 the patient was offered the first cycle of PIPAC with oxaliplatin (OX) at a dosage of 92 mg/m^2 BSA. General condition was reduced with a preoperative Karnofsky Index (KI) of 60%. Intraoperatively there was a high peritoneal cancer index (PCI) score of 21 out of 39 without presence of ascites. Histology revealed a peritoneal regression grading score (PRGS) of 4 (Figure 1). There was no acute or cumulative hematologic, renal, hepatic, or gastrointestinal toxicity detected. Immunosuppressive treatment was maintained with tacrolimus and everolimus. After 5 days, the patient was discharged in good clinical condition. During the following 6-week treatment-free period the patient recovered well and there was an improvement in KI to 80%.

Six weeks later the second cycle of PIPAC OX was performed. PCI-score at that time was 24 out of 39 with 100 mL of newly formed ascites. Histology of peritoneal biopsies showed a median PRGS of 2, indicating a major histological regression (Figure 1). Throughout the PIPAC procedures we encountered no relevant changes of yGT (gamma glutamyl transferase), GOT/ASAT (aspartate aminotransferase), GPT/ALA (alanine aminotransferase), bilirubin or TP (Quick) (Figure 2). There was no acute or cumulative renal toxicity. Of note, PIPAC induced no alterations of tacrolimus or everolimus levels (Figure 3). For 4 months after the second PIPAC application the patient was in a very good health condition and enjoyed a good quality of life. Subsequently, progressive small bowel obstruction developed, and the patient eventually passed away 4 years after cancer diagnosis and 7 months after the first PIPAC cycle.

Patient case 2

The second patient underwent combined kidney-pancreas transplantation in 1994 due to diabetes mellitus type I accompanied by terminal renal failure. Immunosuppressive therapy was maintained with tacrolimus. In May 2017, pancreatic cancer with synchronous PM originating from the patient's own organ was diagnosed. CT scan revealed no extraperitoneal metastasis. After presentation of the case at the multidisciplinary tumor board, the patient received 1 cycle of systemic chemotherapy with gemcitabine and nab-paclitaxel. Therapy was poorly tolerated and had to be interrupted. In June 2017, the patient was offered a first cycle of PIPAC with low-dose cisplatin 7.5 mg/m^2 BSA and doxorubicin 1.5 mg/m^2 BSA (PIPAC C/D). Intraoperative PCI score was 7 out of 39, no ascites was detected at that time. Histology documented a major histological regression after systemic chemotherapy (PRGS 2, Figure 1). During the following 6-week treatment-free period, the patient recovered well and there was an improvement in KI to 70%. The second procedure was uncomplicated, PCI was 5 out of 39 and there was still no ascites. Histologically a PRGS of 1 to 2 was documented (major to complete regression, Figure 1). Throughout the PIPAC procedures, no relevant changes of yGT, GOT/ASAT, GPT/ALAT, creatinine, bilirubin, or TP (Quick) were encountered. PIPAC induced no alterations of tacrolimus serum levels.

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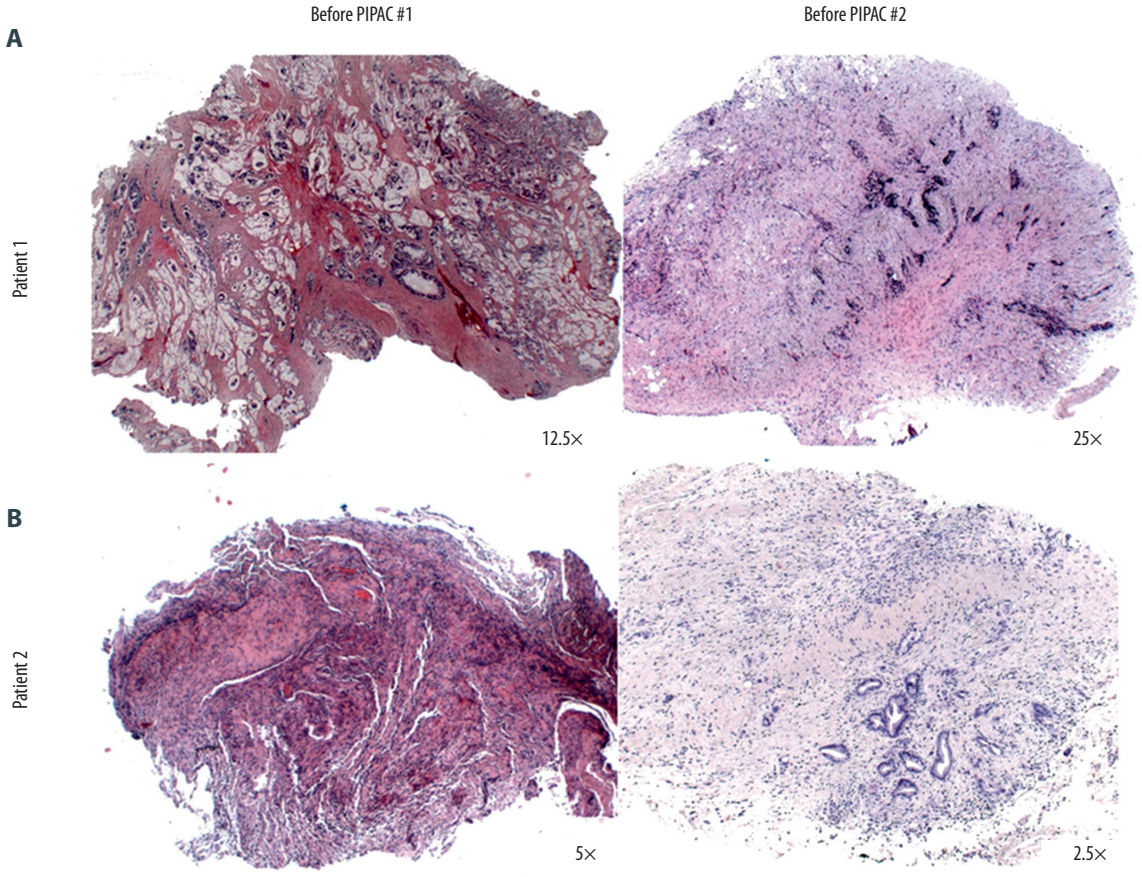

Figure 1. (**A**) Patient case 1: before PIPAC #1 the peritoneal biopsy showed large amounts of vital tumor cells accompanied with minimal local mucin production. No signs of regression (PRGS4). Before PIPAC #2 the peritoneal biopsy showed only minimal amounts of vital tumor cells and higher amount of fibrosis (PRGS 2). (**B**) Patient case 2: before PIPAC #1 the peritoneal biopsy showed only minimal amounts of vital tumor cells and a higher amount of fibrosis (PRGS 2). Before PIPAC #2 the peritoneal biopsy, without vital tumor cells but with large amounts of fibrosis (PRGS 1).

In December 2017, the third PIPAC cycle was administered. Median PRGS was 2 and similar to the former 2 PIPAC procedures it was very well-tolerated, and no alterations of graft function was experienced. At the last follow-up in March 2018, the patient was still alive and was scheduled for the next PIPAC and maintenance therapy with PARP-inhibitor olaparib.

Discussion

Compared with the general population, solid-organ transplant recipients are at increased risk of developing secondary neoplasms *de novo*. Reported reasons for this increased oncological risk are impairment of immunosurveillance, enhancement of chronic viral infection and direct pro-oncogenic effects through immunosuppressive drugs [2].

Development of *de novo* tumors remains a challenge that still needs to be mastered in order to improve long-term outcomes after solid organ transplantation. Together with Dantal et al. [2], we agree that prevention and management of post-transplantation malignancies should be considered as a main goal in transplantation programs. This case report study showed that low-dose PIPAC can induce objective tumor regression of PM in solid organ transplant recipients without inducing organ toxicity or interfering with immunosuppressive therapy.

If these preliminary results are confirmed in larger studies, this first report might be remembered as a significant marker of progress in the field in individual cases, repeated PIPAC induced objective histological tumor response of PM in solid organ transplant recipients under immunosuppression. This observation is in line with previous reports showing high objective histological responses rates for therapy-resistant PM after PIPAC therapy [12]. Recently, a high rate of regression of

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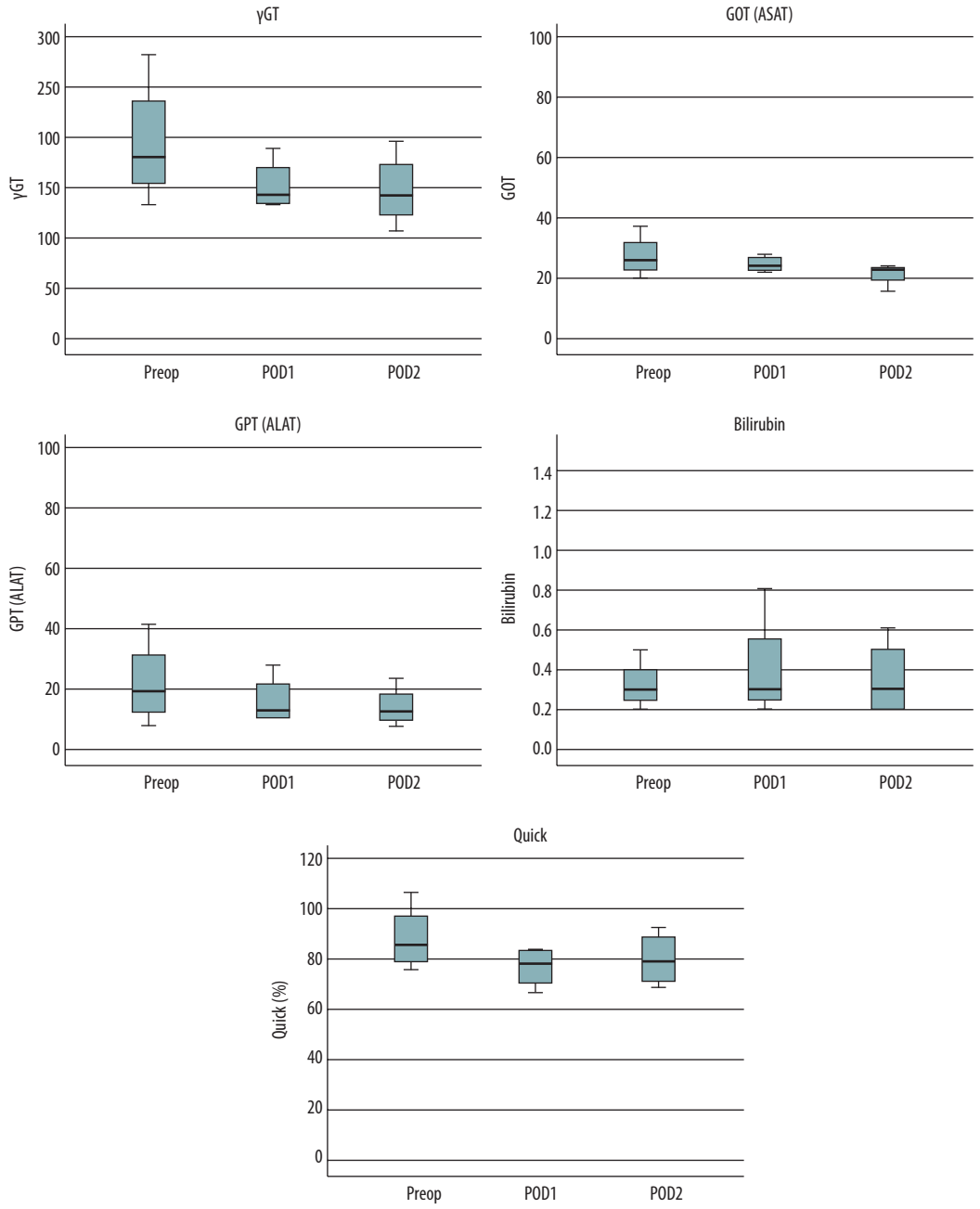

Figure 2. Pre- and post-operative course of laboratory results (γGT – gamma glutamyl transferase; GOT/ASAT – aspartate aminotransferase; GPT/ALAT – alanine aminotransferase; POD – postoperative day).

PM was also demonstrated after PIPAC in hepatobiliary [13] and pancreatic cancer [14,15]. Graversen et al. reported a median overall survival of 11 months in PM of pancreatic origin [15].

Moreover, in contrast to palliative systemic combination chemotherapy, organ toxicity after PIPAC is low. An intensified protocol associating folinic acid, 5-FU, Irinotecan, and oxaliplatin (FOLFIRINOX) was able to achieve a median survival of 11 months but at the cost of a high toxicity rate [16]. In the present report, renal and hepatic function was not altered after PIPAC, and no acute or cumulative toxicity was documented. This confirms previous reports in patient cohorts [8,9] and in a phase-2 ICH-GCP (International Council for Harmonisation-Good Clinical Practice) clinical trial [17].

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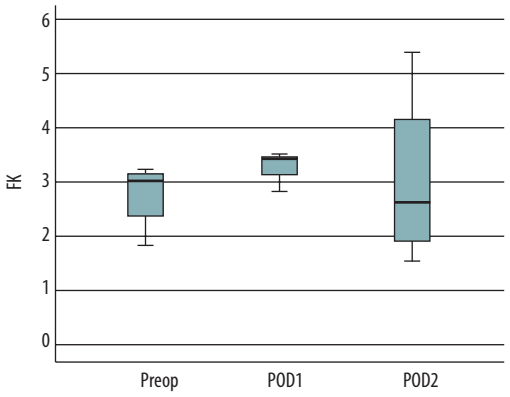

Figure 3. Pre- and post-operative serum levels of tacrolimus (POD – postoperative day).

Another lesson is that PIPAC can be delivered without interfering with plasmatic levels of immunosuppressive drugs and does not require immunosuppressive therapy to be paused. Our data suggest that it is possible to treat PM without compromising immunosuppression, and therefore without increasing the risk of rejection of the transplanted organ.

Finally, patients' general condition improved under PIPAC therapy, as reflected by an increase of the KI in both patients. This observation strengthens previous reports on stabilization or increase of patient-reported outcomes in PM patients receiving PIPAC therapy [18,19].

Conclusions

PIPAC seems to be an appealing tool for solid organ transplant patients with PM who do not meet the criteria for CRS and HIPEC. PIPAC can be applied alone or in combination with systemic chemotherapy [9]. PIPAC can induce an objective histological tumor regression and does not further deteriorate the general condition of a patient. These encouraging data now have to be confirmed in proper clinical studies.

Conflict of interest

MAR holds several patents for PIPAC technologies and receives royalties from Capnomed GmbH, Villingendorf, Germany. The other authors have no conflict of interest to disclose.

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