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Is pressurized intraperitoneal aerosol chemotherapy safe and effective in the treatment of peritoneal metastases from pancreatic adenocarcinoma?

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Abstract

Introduction and purpose: Pancreatic adenocarcinoma (PAC) is the third most common cancer of the gastrointestinal tract in the Western population. Peritoneal metastases (PM) affect 5-10% patients with PAC at the moment of diagnosis and 50% of patients who experience a recurrence after a successful resection. This review aims to evaluate the efficacy of pressurized intraperitoneal aerosol chemotherapy (PIPAC) in the treatment of PM from PAC based on the literature available on PubMed website

Brief description of the state of knowledge: PIPAC is a relatively new method of treatment and the number of studies investigating its application in the treatment of PM from PAC is scarce. Nevertheless, initial findings suggest that PIPAC is linked to 15,6 months of the median overall survival, while standard intravenous chemotherapy reaches only 7,6 months . Furthermore, PIPAC seems to be a fairly safe method, as no grade 3 or grade 4 complications (according to CTCAE v4.0) occurred. However, all of the studies involved an unrepresentative number of patients and they were not free from a selection bias. Moreover, due to the novelty of the PIPAC procedure, it still needs to be properly standardised.

Conclusions: Available data concerning the application of PIPAC in the treatment of PM from PDAC is limited. Large prospective studies consisting of control groups are still lacking. Nevertheless, the results of accessible studies displaying a median OS of participants reaching 14-16,8 months, with no G3 and G4 complications, are encouraging and justify further research.

Key words: aerosol chemotherapy, pancreatic adenocarcinoma, peritoneal metastases, PIPAC

1. Introduction and purpose

Pancreatic adenocarcinoma (PAC) is the third most common gastrointestinal tract cancer in the Western population [1]. It is characterised by an extremely poor prognosis with only 3-7% 5-years survival [2,3]. The reported incidence of PAC is increasing. The only curative treatment is tumour resection. Unfortunately, only 15-20% of patients may undergo a surgery at the time of diagnosis, while another 40% suffer from locally advanced cancer. The rest of patients have already developed metastases - 5-10% of those are localised in the peritoneal cavity [4,5]. Moreover, up to 80% of patients who had a resection are going to experience a recurrence and in 50% of cases it is manifested as a peritoneal metastases (PM) [6,7,8,9].

The treatment of the PM constitutes a challenge. They can induce pain, ascites or gastrointestinal occlusion. The standard treatment of PM from PAC is intravenous palliative chemotherapy. It reaches a median survival of 7,6 months with 5% of severe adverse events [10,11]. The limited response to standard methods of treatment is caused by poor penetration of chemotherapeutic agents into the peritoneal tumour nodules. The PM consist mostly of stromal fraction, which significantly increases the interstitial fluid pressure. Furthermore, they are poorly vascularized, too. Both of these features impair the transport of cytoreductive agents to the cancer cells [12,13].

In order to increase the efficacy of chemotherapy, new ways of delivery have been researched over the last three decades. Hyperthermic intraperitoneal chemotherapy (HIPEC) combined with the cytoreductive surgery (CRS) have shown some encouraging results. This procedure aims to surgically remove most of the tumour tissue from peritoneum and rinse it with warmed up chemotherapy. Even though it may be an effective way of PM treatment, its use is limited by a substantial rate of serious adverse events (52%) and high mortality (5,8%) [14]. What is more, plenty of PDAC patients who are diagnosed with PM may not be eligible for such aggressive treatment, because of their poor overall condition. Hence, innovative and minimally invasive ways of chemotherapy administration are still needed.

Pressurised intraperitoneal aerosol chemotherapy (PIPAC) is a novel and promising method of PM treatment. It has been reported that elevated intra-abdominal pressure

decreases interstitial fluid pressure therefore allowing to obtain higher drug concentration inside tumour tissue [15]. Intraperitoneal delivery makes the penetration distance undoubtedly shorter than during intravenous administration, too. PIPAC is performed during laparoscopy. Chemotherapeutic agents, in the form of aerosol, are being pumped into the peritoneal cavity by a nebuliser inserted through a trocar. It allows for better penetration as well as distribution throughout the peritoneal cavity. Aerosol is later evacuated through a closed ventilation system [16].

Initial findings emphasise the feasibility, safety and efficacy of PIPAC in the treatment of gastric and ovarian cancer. The doses of chemotherapeutic agents used in these studies were as low as 1/10th of regular systemic doses [17,18]. It makes PIPAC significantly less toxic than standard standard treatment. It may be applied when HIPEC + CRS are not a viable option due to age or serious medical state. Additionally PIPAC may be performed multiple times due to minimally invasive administration.

This review aims to evaluate the efficacy of PIPAC in the treatment of PM from PAC based on the literature available on PubMed website.

2. State of knowledge:

2.1. PIPAC procedure

PIPAC procedure has been developed lately and there are only four papers concerning the PIPAC application in the treatment of PM from PAC published [19,20,21,22]. It is also caused by the fact that PM from PAC are not as common as from e.g. ovarian cancer, where 60-80% of patients have PM at the time of diagnosis [5]. PIPAC has been performed in a similar way in all of the available publications. Firstly, the laparoscopy was conducted and the ascites fluid was removed. Then, the peritoneum was visually assessed and rated according to the Sugarbaker Peritoneal Carcinomatosis Index (PCI). Researchers tried to take peritoneal biopsies from all four abdominal quadrants in order to assess the efficacy of treatment based on histological response. Thus a minimal number of two PIPAC procedures had to be performed to describe the histological differences that occured after the applied treatment. Chemotherapy remained in the patient abdomen for 30-35 minutes. The median time of the whole procedure was 92-95 minutes. In all of the studies combination of doxorubicin solution (1.5 mg/m2 in 50 ml NaCl) and cisplatin solution (7.5 mg/m2 w 150 ml NaCl) were used. The median time between PIPAC administrations was 4-6 weeks. Patients

with poor overall medical condition were excluded from the studies. Almost all of the participants received at least one line of chemotherapy before PIPAC treatment [19,20,21,22].

2.2. Brief descriptions of studies

First one was performed by Graversen et al. and published in 2017. Exclusion criteria were ECOG > 2, bowel obstruction, extra-peritoneal metastases. Five patients were included, 3 of them suffered from synchronic PM, the rest experienced a recurrence. All of the patients received ≥ 2 PIPAC procedures. Histological regression was reported in four patients (80%), one patient had stable disease. Histological evaluation of biopsies was based on Peritoneal Regression Grading Score (PRGS). There were no severe complications (G3 and G4 according to CTCAE v4.0). The median overall survival from the day of diagnosis reached 14 months [19].

The second research by Khosrawpiour et al. comes from 2017, too. Patients with Karnofsky Index < 50% or symptoms of bowel obstruction were excluded. 20 participants took part in a study, 12 had synchronic PM while 8 suffered from recurrence after a resection. Only 10 patients received ≥ 2 PIPAC procedures. There were no G3 or G4 adverse events. Histological response was based on the Tumour Regression Scale (TRG). 7 patients (35%) had histological regression, 3 of them did not respond to PIPAC. Median overall survival from the first PIPAC reached 9 months [20].

The third study by Horvath et al is from 2018. Researchers excluded patients with signs of bowel obstruction, extraperitoneal metastases and KI < 60%. There were 6 patients with PAC enrolled. 4/6 patients with PAC had a recurrence after a resection. There were no serious adverse events reported. PRGS score was used. 3 out of 6 patients underwent ≥ 2 PIPAC procedures, one had a stable disease and two experienced a regression. Median time from PM diagnosis to PIPAC was 4 months. Median overall survival from the first PIPAC reached 12,7 months [21].

The last available study by Di Giorgio et al. was published in 2020 . Patients with ECOG >2 and extraperitoneal metastases were excluded. There were 14 participants with PAC, 6 had partial pancreatic resection. No G3/G4 complications occurred. 8 patients were treated with oxaliplatin (92 mg/m2 in 200 ml of 5% glucose solution) instead of standard doxorubicin and cisplatin combination. 8 patients received >1x PIPAC, regression was reported in 7/14 patients based on PRGS. Median overall survival from the diagnosis of PM reached 16,2 months and from the first PIPAC 9,7 months [22].

2.3. Summary of results

Table 1. The summary of results obtained in all of the studies.

		Graversen et al. (5)	Khosrawipour et al. (20)	Horvath et al. (6)	Di Giorgio et al. (14)	All patients (45)
Median OS (months)	od diag.	14	-	16,7	16,2	15,6
	od PIPAC	6	9	12,7	9,7	9,35
severe adverse events rate (G3 G4)		0%	0%	0%	0%	0%
Histological response	all patients.	4/5 (80%)	7/20 (35%)	2/6 (33,3%)	7/14 (50%)	20/45 (44,4%)
	gr. ≥2 PIPAC	4/5 (80%)	7/10 (70%)	2/3 (66,6%)	7/8 (87,5%)	20/26 (77%)
≥2 PIPAC		5 (100%)	10 (50%)	3 (50%)	8 (57%)	26 (57,8%)

The results presented in the described studies are promising and indicate the possible potential of PIPAC treatment. The mean of reported median overall survival periods reached 15,6 months. It almost doubled the outcome of standard treatment for the PM from PAC. Furthermore, doctors did not encounter any severe adverse events induced by PIPAC. The most common complications were: abdominal pain and PONV (postoperative nausea and vomiting). Researchers did not come across any procedure-related deaths, either. Both of these findings may suggest a high safety profile as they are in line with other studies on PIPAC.

The mean histological response reached 44,4% and it is inferior to 50-70% observed in the studies on the treatment of PM from gastric or colorectal cancer[23,24]. However, the verification of histological response could be done only in patients who were subjected to ≥2 PIPAC procedures. The histological regression rate reached 77% among patients who experienced ≥2 cycles of treatment. Nevertheless, the percentage of patients who received only one PIPAC (43,2%) is worrying.

All of the previously described studies relies on the small number of participants. What is more, they suffer from a selection bias because the patients were recruited based on their overall condition, previous treatment and lack of extraperitoneal metastases. Additionally, patients received various types of systemic treatment, sometimes even in

between the PIPAC procedures and it is difficult to estimate how it affected the results. None of the studies consisted of a control group, too. Therefore, the obtained data has to be interpreted with caution.

Only 57,8% of patients from all of the studies were exposed to ≥2 PIPAC procedures. The most common reasons for discontinuation of the treatment were: clinical deterioration, cancer cachexia, ileus or subileus symptoms and exitus letalis. Di Giorgio et al. reported that all of the patients with ascites volume > 2000 ml were not able to undergo more than one PIPAC procedure, which may indicate late and unresponsive to treatment stage of LAP [22]. Those observations suggest that a proper selection of patients can play a key role in safe and efficient application of PIPAC.

The establishment of an adequate scale to measure the PIPAC effectiveness is essential. All of the researchers agree that Sugarbaker PCI assessment is not a suitable tool for PIPAC evaluation [19,20,21,22]. It is unreliable due to peritoneal adhesions in patients who underwent resection and diffuse peritoneal sclerosis caused by repetitive PIPAC administrations. Three out of four aforementioned studies [19,21,22] relied on histological evaluation based on Peritoneal Regression Grading Score (PRGS) and one on Tumour Regression Scale (TRG) [20]. In order to objectively compare the results of studies on the PIPAC treatment, one scale has to be chosen based on the thorough examination.

The standardisation of PIPAC procedure constitutes a major problem [21,22]. Larger studies are required to establish the optimal doses of chemotherapeutic agents, time of exposure to aerosol, the value of pressure inside peritoneum and the length of period in between the PIPAC administrations.

3. Conclusions

PIPAC is a promising treatment that may induce histological regression of PM from PAC. Initial studies suggest that PIPAC can significantly improve the median OS reached by patients in comparison to standard systemic chemotherapy. It is also linked to significantly lower toxicity, too. Unfortunately, due to the limited number of patients, selection bias and lack of standardisation, the objective clinical impact of PIPAC cannot be estimated. Nonetheless, the obtained results are encouraging and justify further research involving larger groups of participants.

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