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Symptom Palliation by PIPAC for Peritoneal Carcinomatosis from the Gastrointestinal Tract

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Abstract

Background: PIPAC is an innovative palliative care treatment for Peritoneal Carcinomatosis (PC). The purpose of this study is to assess the impact of PIPAC with oxaliplatin on symptoms (occlusion, ascites) of peritoneal metastasis from gastrointestinal tract cancer with assessment of early markers of tumor response.

Methods: All consecutive PIPAC with oxaliplatin per formed in a comprehensive cancer center between 2017 to 2020 were included. Cox analysis was used to identify time to Worsening of Symptoms (TWS) factors.

Results: 25 patients underwent 85 PIPAC (Median period: 105 days). The primary was colorectal, gastric, and small bowel cancer in respectively 13, 10, and 2 cases. The median TWS and Overall Survivals (OS) after the first PIPAC were respectively 207 and 309 days. No early markers of tumor response (lower PCI or histological grading during PIPAC) were associated with TWS. In univariate analysis, TWS factors were extended PC (PCI>20, p=0.03) and presence of symptoms at first PIPAC (p=0.03). In multivariate analysis, these factors did not reach significance. TWS was particularly short (<3 months) for patients with obstructions.

Conclusion: PIPAC with oxaliplatin provides prolonged control of carcinomatosis-related symptoms but seems poorly effective to control pre-existing PC obstructions. No predictive factors extending TWS were identified.

Keywords: Peritoneal carcinomatosis; PIPAC; Oxaliplatin; Symptom; Obstruction; Palliative care

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Introduction

Worldwide in 2018, 2.8 million cases of gastrointestinal carcinomas (stomach, small bowel, colon, and rectum) were diagnosed [1]. Peritoneal Carcinomatosis (PC) occurred in 10% to 15% of these patients [2] and was associated with poor prognosis [3]. PC is resistant to systemic chemotherapy. Complete Cytoreductive Surgery (CRS) can improve long-term survival with a 5-year Overall Survival (OS) rate of 20% to 50% [4-8]. However, this treatment is possible for less than 10% of patients and the vast majority (90%) are treated with a palliative intent. Palliative treatment of PC has to manage frequent complications such as bowel dysmotility or obstruction, abdominal pain, ascites, ureteral or biliary obstruction. These complications have a major impact on patient quality of life. Malignant obstruction is the main challenge in palliative care for PC. Oral food intake is somewhat improved by medical treatment whilst surgical treatment has high morbidity and mortality [9-12]. The goal of new palliative treatments for PC is to relieve symptoms and prolong symptom-free survival in order to improve quality of life. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) is an innovative surgical procedure proposed as a new palliative treatment for PC. This technique of repeated Intraperitoneal (IP) chemotherapy by laparoscopy is safe and standardized [13]. The survival and response rates are promising [13]. The procedure requires short hospitalization but increased nursing and resources. The brief period of discomfort following PIPAC is only justified where there is relevant clinical benefit for patients. The purpose of this study was to assess the impact of PIPAC on specific symptoms (occlusion, ascites) of PC from

the gastrointestinal tract and analyze time to worsening of symptoms factors in an attempt to identify early markers of tumor response.

Patients and Methods

Patient selection

All consecutive patients who underwent PIPAC procedures for PC from the gastrointestinal tract in the Institut de Cancérologie de l'Ouest, Saint-Herblain, France, from November 2017 to July 2020 were retrospectively analyzed in intention to treat. The indications of PIPAC treatment were determined by a multidisciplinary clinical committee. The inclusion criteria for PIPAC treatment were patients with PC from histologically confirmed gastrointestinal tract cancer; at least 3 months of systemic chemotherapy; advanced peritoneal carcinomatosis with Peritoneal Cancer Index (PCI) assessed by laparoscopy over 5, 13, and 15 for, respectively, gastric, small bowel, and colorectal primaries; tumor resistant to intensified (triple drug regimen) systemic chemotherapy; life expectancy >3 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate organ function; no peripheral neuropathy grade >1, no known hypersensitivity to oxaliplatin, and no active uncontrolled infection.

The PC-related symptoms assessed were obstruction and intractable ascites. Worsening obstruction from PC was defined as occlusion of the intraperitoneal tract (bowel, ureter or biliary tract) requiring medication with steroid or decompressive interventions such as nasogastric tube, intraluminal stenting, surgical bypass or stoma. Worsening ascites was defined as ascites requiring decompression paracentesis.

This observational study was performed in accordance with the Declaration of Helsinki and all patients gave their consent to participate.

Operative technique

One hour to 24 h before PIPAC, we delivered systemic intravenous leucovorin 20 mg/m^2 and 5-FU 400 mg/m^2. This treatment schedule was previously justifying [14].

After insufflation of 12 mmHg of capnoperitoneum, three balloon trocars were placed. Explorative laparoscopy was performed as usual and Peritoneal Cancer Index (PCI) was determined. Parietal biopsies were taken for histological response assessment according to Peritoneal Regression Grading Score (PRGS). A nebulizer (MIP, Reger Medizintechnik, Rottweil, Villingendorf, Germany) was connected to a high-pressure injector (Accutron CT-D, Medtron, Saarbrucken, Germany) and inserted into the abdomen through a trocar. A pressurized aerosol containing oxaliplatin at a dose of 90 mg/m^2 to 140 mg/m^2 body surface area in 150 ml of 5% dextrose solution was applied. The system was then kept in a steady state for thirty minutes (application time). Toxic aerosol was exhausted over a closed system. Trocars were retracted.

Treatment schedule and follow-up

Patients received PIPAC procedures at four- to six-week intervals until disease progression, unacceptable toxic effects, major response allowing CRS, major intraperitoneal adherences limiting laparoscopy feasibility, worsening of patients 'performance status, or patient refusal.

Post-PIPAC follow-up was repeated every month until death. Physical examinations were performed at each patient visit plus thoracoabdominal CT scans every three months. CT scans were not systematic when patient shad altered general conditions (ECOG>2). Additional physical examinations were determined by symptoms in the Palliative Care Unit.

Statistical analysis

Patients treated with PIPAC were prospectively recorded in a specific database. Descriptive analyzes we represented as the number for qualitative variables or median for quantitative variables.

Time to Worsening of Symptoms (TWS) was calculated from the date of first PIPAC to the date of worsening of symptoms or death. Survival curves were generated by Kaplan–Meier methods and compared using the log-rank test. Univariate Cox regression analysis was used to assess the relationship between different factors and SFS. A p-value of ≤ 0.05 was considered significant. Significant covariates on univariate analyses were included in the final multivariate Cox regression model. All analyzes were conducted using XLSTAT Life Sciences v2020.5.

Results

Baseline characteristics

From November 2017 to July 2020, 25 consecutive patients receiving 85 PIPAC procedures with oxaliplatin were analyzed.

The clinical and disease characteristics of the analyzed cohort are summarized in Table 1.

The median interval between PC diagnosis and first PIPAC was 228 days (41 to 810). The median number of PIPAC was 3 (2 to 5) over a period of 105 days (27 to 154).

Three patients had symptoms before first PIPAC; one had refractory ascites, and two small bowel obstructions requiring corticosteroids. The median variation of PCI between first and second PIPAC was -4% (-64% to +50%). Four patients with major histological response (n=3) and low PCI (n=1) were planned for CRS. Three patients underwent CRS and one had exploratory laparotomy because the PC remained unresectable.

Clinical course and survival

The median follow-up was 234 days (range 57–976). The median TWS and OS were respectively 207 and 309 days (Figure 1). The worsening symptoms were intestinal tract obstruction, ascites, biliary and ureteral obstruction in respectively 14, 2, 1, and 1 case. No patient

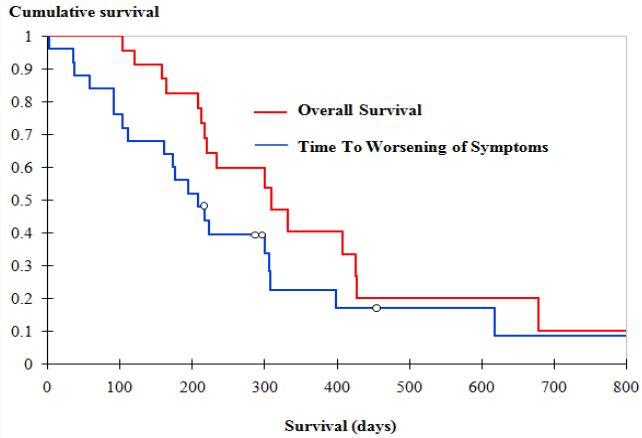

Figure 1: Overall survival and time to worsening of symptoms for the entire series.

Table 1: Patients, tumors, and treatment characteristics.

Characteristics	
Median age, years (range)	55 (42–69)
Gender male/female (n)	10/15
Primary cancer (n)	
Gastric	10
Small bowel	2
Colorectal	13
Primary tumor in situ	10
Median days from PC diagnosis and PIPAC (range)	228 (41–810)
Histology	
Mucinous	6
Signet ring cell	5
Low grade	11
High grade	3
Previous number of bi or triplet systemic chemotherapy cycles, median (range)	6 (4–18)
Previous number of patients received systemic oxaliplatin chemotherapy, median (range)	20
Drug regimen at first line (n)	
Double	10
Triple	17
Symptoms at first PIPAC (n)	3
Initial median PCI (range)	20 (6–39)
Number of PIPAC procedures, median (range)	3 (2–7)
Total cumulative IP dose of oxaliplatin during PIPAC (mg), median (range)	619 (254–1316)
Median PCI at second PIPAC (range)	17 (5–39)
Histological regression score at second PIPAC(n)	
PRGS 1–2	9
PRGS 3–4	12
Not assessable, heterogeneous or missing data	4
Signet ring cell histology (n)	5
BRAF mutated if primary colorectal cancer (n)	0
KRAS mutated if primary colorectal cancer (n)	9
Number of complete cytoreduction CC0 (n)	3

PIPAC: Pressurized Intraperitoneal Aerosol Chemotherapy; PCI: Peritoneal Cancer Index; PRGS: Peritoneal Regression Grading Score

with obstruction had surgical decompression and one underwent ureteral stenting.

Among the three patients with symptoms before PIPAC, two had intestinal obstructions. The occlusion persisted in one case and improved for three months before recurring in the other. The patient with refractory ascites improved for more than six months and required further paracentesis 191 days after the first PIPAC session.

In univariate analysis (Table 2), the factors associated with TWS were extended carcinomatosis (PCI>20, p=0.031) and presence of symptoms at first PIPAC (p=0.028). In multivariate analysis (Table 2), these factors did not reach significance.

The risk of worsening symptoms was reduced by CRS without statistical significance. Patients with symptoms at first PIPAC, PCI>20, and CRS had respectively a median TWS of 91, 161 and 297 days (Figure 2, 3).

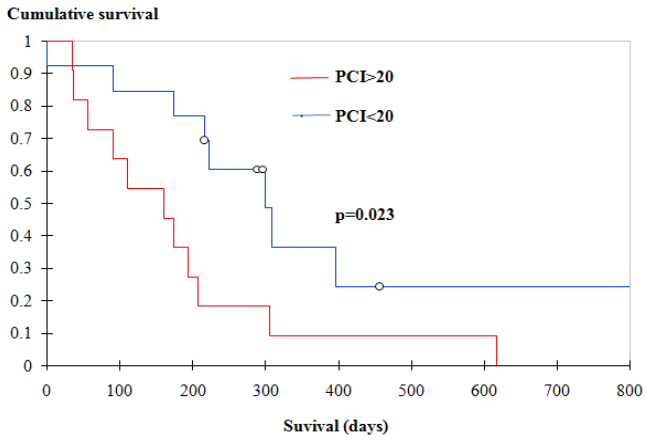

Figure 2: Time to worsening of symptoms according to peritoneal carcinomatosis extension assessed by PCI.

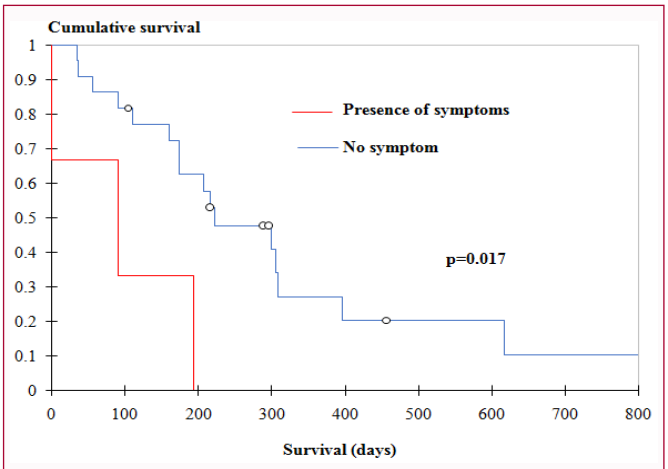

Figure 3: Time to worsening of symptoms according to the presence of symptoms at the first PIPAC.

Discussion

Palliation is a major hallmark of new treatments such as PIPAC for PC. PC predisposes to specific and severe functional evolutions such as obstruction or ascites. Bowel obstruction is frequent in carcinomatosis progression and can persist for several months before death with a major impact on quality of life [15,16]. Control of symptoms is a step forward in measuring the success of PIPAC. This additional outcome has to be considered in PC supportive care because quality of life is dependent on many factors unrelated to oncologic treatment [17].

In our series, symptoms were controlled by PIPAC for more than 6 months (207 days). Our results are consistent with prior reports. Physical scores such as nausea, vomiting or fatigue were maintained or improved in patients receiving repeated PIPAC applications [18-20]. There was no deterioration of functional scores, including physical, emotional, cognitive, role, and social scores during all PIPAC treatment lengths [18]. Our results suggest that PIPAC provides clinical benefits and should be included in the overall palliative care strategy.

The median OS was ten months in our series. This OS was reasonable but less encouraging than other series in the literature

Table 2: Univariate and multivariate regression analysis for time to worsening of symptoms.

	Univariate			Multivariate		
Covariates	**Hazard Ratio**	**95% CI**	**p**	**Hazard Ratio**	**95% CI**	**p**
Symptoms at first PIPAC						
No	ref			ref		
Yes	4.359	(1.168–16.262)	0.028	3.252	(0.86–12.293)	0.082
Gastric primary						
No	ref					
Yes	0.87	(0.34–2.23)	0.772			
High dose of IP oxaliplatin (140mg/m²)						
No	ref					
Yes	0.213	(0.03–1.499)	0.12			
Total cumulative IP oxaliplatin (mg)	0.999	(0.997–1.002)	0.355			
Primary in situ						
No	ref					
Yes	0.889	(0.354–2.229)	0.801			
Signet ring cell						
No	ref					
Yes	1.5	(0.473–4.759)	0.491			
Histological high grade						
No	ref					
Yes	0.58	(0.082–4.111)	0.586			
Interval between carcinomatosis diagnosis and first PIPAC (days)	1	(0.999–1)	0.146			
Systemic first-line chemotherapy before PIPAC						
Double drug regimen	ref					
Triple drug regimen	0.135	(0.775–6.652)	0.135			
Number of systemic chemotherapy cures before PIPAC	1.044	(0.931–1.171)	0.459			
Number of systemic chemotherapy lines before PIPAC						
One	ref					
More than one	1.573	(0.558–4.433)	0.391			
Number of PIPAC sessions						
One or two	ref					
More than two	0.749	(0.266–2.108)	0.391			
PCI						
PCI<20	ref			ref		
PCI>20	2.82	(1.101–7.226)	0.031	2.544	(0.98–6.6)	0.055
Delta PCI before first and second PIPAC						
Less than 20%	ref					
More than 20%	0.781	(0.256–2.377)	0.663			
PRGS score at second PIPAC						
Good response (1–2)	ref					
Low response (3–4)	1.147	(0.403–3.268)	0.797			
Complete cytoreductive surgery						
No	ref					
Yes	0.004	(0.00–9.581)	0.164			

PIPAC: Pressurized Intraperitoneal Aerosol Chemotherapy; PCI: Peritoneal Cancer Index; PRGS: Peritoneal Regression Grading Score

ranging from eight to nineteen months [13]. However, direct comparison of these studies is difficult, underlining the need for results from ongoing prospective and/or comparative studies with consistent selection criteria [15,24].

On Cox univariate analysis, our study showed that the presence of symptoms at first PIPAC was significantly related to early failure of symptom control. Patients with obstructions at first PIPAC had no improvement or early recurrence (less than three months). Some authors have suggested that PIPAC is unable to relieve occlusion [21]. Like other authors [21-25], we believe that PIPAC is not a salvage therapy to treat obstruction due to its low effectiveness and low symptom-free life expectancy.

The impact of PIPAC on refractory ascites and obstruction seems different. Control of refractory ascites by PIPAC was prolonged in one patient to 191 days without paracentesis. IP chemotherapy was shown in the literature to be an effective as treatment. One session of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) makes it possible to control malignant refractory ascites for more than three months [26,27]. PIPAC is another technique of IP chemotherapy administration which controls or decreases significantly ascites volume during the therapeutic period [19]. Prospective studies on ascites control by PIPAC are an unmet need. The mechanisms whereby ascites and not obstruction is resolved through the use of IP chemotherapy have not been clearly explained. Some hypotheses can be suggested. Firstly, massive ascites large the volume of the abdominal cavity, allowing IP chemotherapy diffusion. In contrast, bowel dilatation is usually caused by areas 'plastered' by extensive mesenteric or omental spread. These conditions limit the volume and expansion of the abdominal cavity by capnoperitoneum and so limit IP chemotherapy diffusion.

Secondly, during intestinal obstruction, the intraluminal hypertension leads to a vicious circle of distension–secretion exacerbating occlusion [28]. IP chemotherapy could have no impact on the obstructive part of this inflammatory response in the intestinal epithelium.

In this study, extended carcinomatosis was preponderant for symptom occurrence and the initial PCI was the most important prognosis factor of TWS. A high PCI is well-known to be the worst prognostic factor of PC in the literature [29]. However, in our series, patients with initial high PCI>20 had 5 months of symptom control, consistent with patients with short median survival in the literature [3]. Finally, our study suggests that the only appropriate selection criterion to contraindicate PIPAC treatment is the presence of obstructive symptoms.

No early predictive factors of PIPAC efficacy were identified in our series: lower PCI or PRGS on biopsies taken during the second session were not associated with longer symptom control. Our data are consistent with the Benzerdjeb et al. study, which found no prognostic correlation of PRGS or PCI during PIPAC for gastrointestinal PC [30]. Several limitations may explain our results. There is significant disparity of 15% to 17% [31,32] between the surgeon's macroscopic diagnosis and the histological diagnosis. Repeated IP chemotherapy with PIPAC increases the difficulties of interpreting tumor spread. The peritoneal sclerosis induced by oxaliplatin [33], peritoneal scarring of tumor necrosis, and additional adherences along the PIPAC sessions complicate the interpretation of abnormal areas of the peritoneum. The effectiveness and reproducibility of PCI scoring during laparoscopy throughout PIPAC treatment are unknown and questionable.

PRGS also has some limitations. The number of samples is limited to one to three non-adhering abdominal regions and does not reflect the whole abdominal cavity's tumor response. IP chemotherapy diffusion is heterogeneous [34,35], with PIPAC and chemotherapy not reaching the areas 'plastered' by extensive mesenteric or omental spread.

CRS was not associated with prolonged TWS despite a significant Hazard Ratio. CRS reduces the risk of symptom occurrence by 99%. This data is clinically relevant despite no statistical significance. Complete CRS is a well-known major prognosis factor of survival in the literature [8,29]. Although modern and intensified chemotherapy like PIPAC improves tumor control and TWS, radical surgery is the only treatment to achieve long-term disease control [8]. However, the conversion rate of diffuse PC to resectable localized disease remained low in our series (12%) and close to the rate (18%) achieved in Alyami's study [36]. PIPAC remains mainly a palliative chemotherapy with a median survival ranging from 85 days to 20 months in the literature [36]. These low survivals in the literature data underline the importance of considering symptom control and comfort as the major goal of treatment.

Our study's main limitation is a small sample and follow-up that is too short to draw strong conclusions about overall survival. Our results should be taken with caution. However, our treatment protocol and population selection are consistent, with a precise definition of symptoms.

Conclusion

PIPAC with oxaliplatin provides prolonged control of carcinomatosis-related symptoms. The treatment seems poorly effective for patients who already have obstructive symptoms. This may provide important information on the use of PIPAC in early palliative treatment phases.

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