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Research article

Metronomic Chemotherapy for Pre-Treated Metastatic Pancreatic Cancer

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Abstract

Background: A prospective observational trial was performed to assess whether metronomic chemotherapy with a novel benzene-poly-carboxylic acids polymer with a cis-diammineplatinum (II) complex (BPC1) was successful for pretreated metastatic pancreatic cancer. Methods: Patients were given a daily intramuscular injection of 0.035 mg. BPC1/kg bodyweight for 32 days. CT scans were done at screening and after 32 days. The results were assessed according to RECIST. Toxicity according to CTC-NCI, QoL according to EORTC-QLQ-C30 and blood analyses was recorded at screening and after 16 and 32 days. Findings: 16 patients were recruited, but 2 died before they had started treatment. Additional 2 patients died during the treatment period. The study sample for efficacy analysis thus consisted of 12 patients. The mean Sum Lesions declined slightly from 47.3 mm at screening to 46.3mm after 32 BPC1 injections. The result was classified as stable disease or better in 9 patients or 75% [95% CI: 42.8–94.5] while 3 patients had progressive disease. The QoL variables" Physical activity problems" and "Discomfort last week" declined significantly ($p<0.01$) while "Health and quality of life " increased significantly ($p<0.01$) from screening to day 32 of BPC1 treatment. The sum CTC-NCI score increased non-significantly ($p=0.16$) from screening to day 32. A total of 30 adverse reactions were reported, of which 20 were assessed as probably related to BPC1. The severity degree was mild in 13 cases, moderate in 5 and severe in 2 cases. Conclusion: Short-term metronomic BPC1 therapy was safe, improved quality of life and may suppress pancreatic cancer growth.

Keyword: Metronomic therapy, platinum complex, BP-C1, metastatic pancreatic cancer

Introduction

From a therapeutic and prognostic perspective pancreatic cancer (PaC) is a tremendous challenge. The majority of patients progresses to either locally advanced or metastatic disease in the asymptomatic phase. Surgical excision is the sole curative option and has a five year survival rate of 20%, but this option is only possible in 15-20% of the patients [1]. For metastatic disease the five year overall survival (OS) remains at 2% with a median life expectancy of <1 year with current treatments [2]. Worldwide, there were 460,000 new cases in 2018 [3]. PaC was the only examined neoplasm with a negative outlook in both sexes of all ages in the EU as a whole, and deaths due to pancreatic cancer increased from 73,439 in 2009 to approximately 82,300 in 2014 [4]. In the Unites States, PaC may become the second leading cause of cancer-related death in the next decade [5].

Guidelines recommend that initial systemic chemotherapy given at maximum tolerated dose (MTD) designed to kill tumor cells should be offered for both local advanced and metastatic disease [1, 2]. In 1997, gemcitabine monotherapy replaced 5-FU as the standard of care for metastatic disease thanks to the superior clinical benefit and small survival advantage [6]. The next major improvement came with the demonstration that the FOLFIRINOX regimen resulted in a median OS of 11.1 months compared with 6.8 months in the gemcitabine group [7]. However, the patients in this study were carefully selected with PS of 0-1 and a normal serum bilirubin level, and FOLFIRINOX had a higher toxicity and more AEs than gemcitabine. Finally, a combination regimen with gemcitabine plus nab-paclitaxel proved superior to gemcitabine monotherapy. Thus, the median OS was 8.5 months in the gemcitabine plus nab-paclitaxel group compared to 6.7 months in the gemcitabine group [8]. Today, FOLFIRINOX is recommended by ASCO for treatment of metastatic patients with good performance status [2], while ESMO recommends FOLFIRINOX or gemcitabine plus nab-paclitaxel [1]. Both societies recommend gemcitabine

monotherapy in patients with a less favorable starting point including an elevated serum bilirubin level, while the treatment has to be case-by-case based in patients with a significant disease burden and a short life expectancy. Second-line therapy is a balance between risk and benefit. The options are gemcitabine plus nab-paclitaxel, or gemcitabine monotherapy after first-line FOLFIRINOX treatment. Fluorouracil, oxaliplatin, irinotecan or nanoliposomal irinotecan are candidates after gemcitabine plus nab-paclitaxel or gemcitabine monotherapy. No data are available to recommend any third-line therapy.

Metronomic chemotherapy has shown that repetitive low doses of anticancer drugs can suppress tumor growth with acceptable toxicity and constitutes an additional opportunity to treat the disease [9]. The novel compound BPC1 contains cis diammineplatinum (II) complex and previous studies in pretreated metastatic breast cancer from our group showed that metronomic BPC1 treatment suppressed tumor growth, improved QoL and had mainly mild to moderate side effects [10, 11]. Because clinical trial participation in third-line therapy of PaC has been encouraged [2] we designed this prospective observational trial to establish the short term efficacy and tolerability of metronomic BPC1 therapy in metastatic PaC patients who had exhausted recommended chemotherapy.

Methods

Study design and participants

This was a prospective observational trial. Patients of both sexes suffering from histologically verified metastatic PaC who had previously undergone guideline- recommended chemotherapy and had an expected survival time of at least three months were treated in Menoufia University Hospital, Egypt. Patients with bilirubin >136 µmol/l, serum creatinine >120 µmol/l, Hgb <6.0 mmol/l, platelet count <100,000/mm3, leucocytes <3 x 109/l or an abnormal coagulation capacity were excluded from the trial. Verified brain metastasis, synchronous cancer, clinical significant abnormal ECG, a Karnofsky score of <60%, systemic treatment with corticosteroids or other immunosuppressive drugs during the previous 21 days, and uncontrolled bacterial, viral, fungal or parasite infection were additional exclusion criteria. The trial protocol was approved by the regional scientific ethical committee (IRB protocol no 0067/2013) and all patients provided oral and written informed consent for experimental treatment.

Procedures

Potential participants underwent a screening phase of maximum seven days. Contrast enhanced thoraco-abdominal CT scans and blood sampling was performed. Toxicity was recorded according to CTC-NCI Version 2.0 [12] and sum CTC-NCI score and maximum score were used as variables. Patient-reported quality of life (QoL) according to QLQ-C30 questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) [13] was obtained. The QoL-variables extracted from the questionnaires were the sum-score variables “Physical activity problems” (C1 – C5), “Discomfort last week” (C6 – C28) and “Health and life quality” (C29 – C30). A daily intramuscular injection of 0.035 mg. BPC1/kg bodyweight started on day 1 and continued for 32 days. Clinical examination, blood sampling, toxicity recording and QoL reporting took place after 16 and 32 days of treatment, designated as day 16 (16±2 days) and day 32 (32±2 days), respectively. CT scans were undertaken at day 32 and the treatment response compared to baseline was classified according to RECIST 1.1 criteria [14]. If patients wanted it, the treatment could be continued outside of protocol for a further 28 days ended with a CT scan. The primary endpoint was treatment response. Secondary endpoints were tolerability and QoL.

Statistical analysis

All assumed continuously distributed variables are given as mean values with Standard Deviation (SD) in brackets and 95 % confidence intervals and calculated in accordance with the Student procedure [15]. Discrete and categorical variables are presented in contingency tables [16]. Changes in discrete variables are given in shift-tables. In case of missing observations, the procedure ‘Last Observation Carried Forward’ (LOCF) was used [17]. Changes were considered significant for p-values less or equal to a level of 0.05. Analysis of Variance (ANOVA) was performed on assumed continuously distributed variables with the initial observation as covariate [18]. A Contingency Table Analysis was used for changes in discrete and categorical variables. Data for all patients were correctly enrolled on trial for analyses of primary and secondary outcomes. SAS version 9.4 was used for statistical analyses. The study is registered with ClinicalTrials.gov, identifier NCT03627390.

Results

16 patients underwent screening for inclusion, but 2 died prior to start of the trial treatment. In accordance with Good Statistical Practice, 14 patients who started injection therapy were included in the safety analysis. However, 2 of the 14 patients died after four and seven injections, respectively. A review of the records revealed that both patients were erroneously included due to very short life expectancy. Thus, the study sample for response and QoL analyses consisted of 12 patients (Table 1). In total, 25 concomitant treatments were recorded in 11 of the 12 patients before the start of the trial treatment (Table 2).

Three of the 12 patients in the study sample died before finalizing the trial treatment. Among these, one patient with clinical evidence of rapidly PD died on day 22. The second patient died on day 25 due to end-stage renal disease, and the third patient died of hematemesis on day 28. In accordance with the RECIST criteria, these 3 patients were classified as PD. The mean Sum Lesions in the remaining 9 patients decreased slightly from a baseline level of 47.3 mm to 46.3mm after 32 BP-C1 injections (Table 3). All 9 patients were classified as SD or better, resulting in a Disease Control Rate (DCR) of 75% [95% CI: 42.8–94.5]. All of these patients chose to continue BPC1 treatment outside protocol, but CT scans after 28 days of further treatment were only achieved in 4 patients. The mean Sum Lesions for these 4 patients declined significantly (p=0.03) from 40.0 mm at screening to 14.0 mm after 32 plus 28 days [95% CI: 6.5–21.5].

"Physical activity problem" declined significantly (p<0.01) from 14.3 [95% CI: 12.2–16.3] at baseline to 8.3 after 16 days and to 7.6 [95% CI: 6.5–21.5] at the end of treatment (Figure 1a). The same pattern was obtained for "Discomfort last week" (Figure 1b). Thus, discomfort declined significantly (p<0.01) from 61.3 [95% CI: 53.4–69.3] at screening to 35.8 after 16 days and 36.2 [95% CI: 32.2–40.1] at day 32. "Health and quality of life" improved significantly (p<0.01) from 5.1 [95% CI: 3.8–6.4] at screening to 9.5 and 9.9 [95% CI: 8.6–11.2] after 32 days of BPC1 treatment (Figure1a).

Max CTC-NCI score increased from screening to day 32 in 4 patients and decreased in one. Sum CTC-NCI score increased non-significantly from 9.8 [95% CI: 4.6–15.0] at screening to 12.3 at day 16 (p=0.30) and 13.4 [95% CI: 5.5–21.3] at day 32 (p=0.16).

In total, 30 AEs were reported during the treatment. 20 were classified as probably, possible or definitely related to BPC1. The severity degree of AEs related to BPC1 was mild in 13 cases, moderate in five and severe in two cases (Table 4). During BPC1 treatment, 10 concomitant treatments were given to seven patients (Table 2).

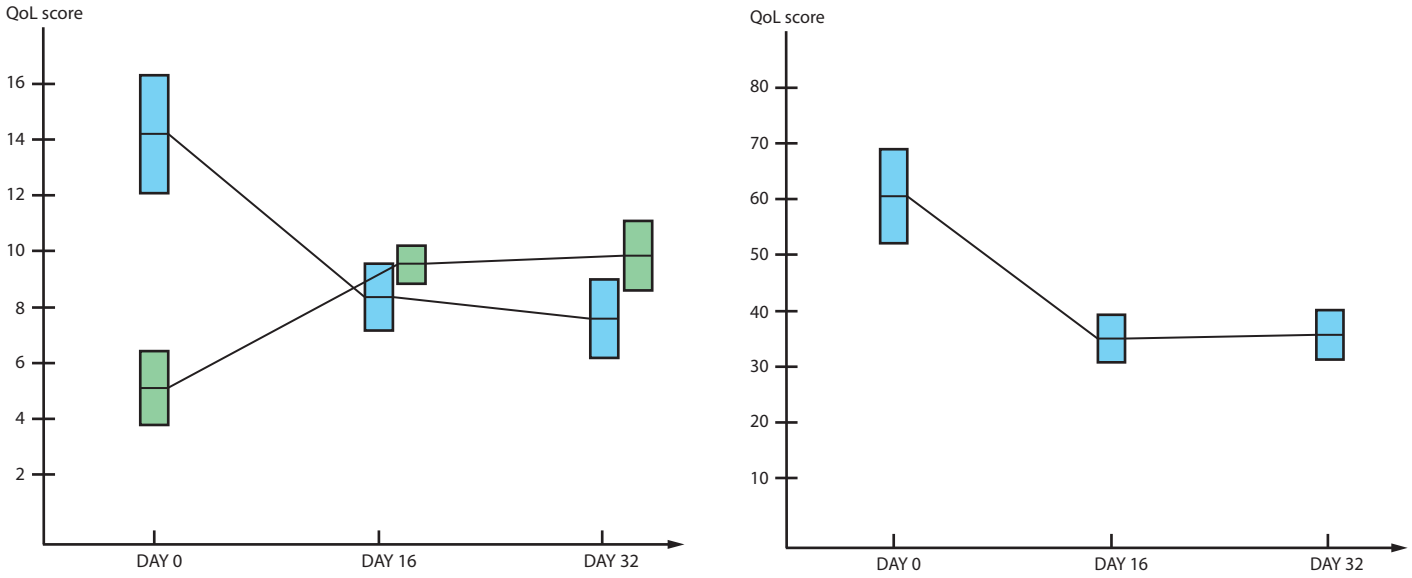

Figure 1. Development in quality of life during BPC1 treatment. The results in 12 patients are given as mean values with 95% confidence intervals in the columns. 1a): The development in "Physical activity problems" is shown in blue columns, and "Health and quality of life" in green columns. 1B): The development in "Discomfort last week" is shown in blue columns.

Table 1. Demographic data of all screened patients (n=16) and treated patients (n=12). The results are given as mean with SD in brackets, 95% confidence interval of the mean, median and total range

Sample	Factor	Mean (SD)	Median	Total Range
Screened patients (n=16)	Age (years)	61.8 (8.8)	63.3	41.5 – 75.7
	Disease duration (months)	1.8 (2.6)	0.9	0 – 9.2
	Weight (kg)	68.4 (12.3)	72.0	48 - 92
	Height (m) *	1.69 (0.08)	1.68	1.56 – 1.86
	Body Mass Index (kg/m2)*	23.9 (3.4)	24.9	18.1 – 29.7
Treated patients (n=12)	Age (years)	62.3 (9.6)	63.3	41.5 – 75.7
	Disease duration (months)	2.2 (2.9)	1.0	0 – 9.2
	Weight (kg)	70.7 (12.0)	74.0	50 - 92
	Height (m) *	1.70 (0.09)	1.68	1.56 – 1.86
	Body Mass Index (kg/m2)*	24.4 (3.1)	25.0	19.1 – 29.7

* Height missing for one patient

Table 2. Indication of concomitant treatment started prior and during the study

Indication	Prior to start of BPC1	During BPC1 treatment	Total
Gastritis	5	0	5
Nausea	1	0	1
Vomiting	1	3	4
Indigestion	3	0	3
Gastric disorder	1	0	1
Constipation	0	1	1
Diabetes Mellitus	2	0	2
Pain	6	1	7
Dementia	0	1	1
Cognitive disorder	0	1	1
Hypertension	2	0	2
Atrial fibrillation	1	0	1
Deep Venous Thromb	1	0	1
Infection	1	1	2
Fever	0	1	1
Weakness	1	1	2
Total	25	10	35

Table 3. Observed change in Sum Lesions diameters in millimeter and percent. The results from 12 patients are given as mean values with Standard Deviation (SD) in brackets and 95%confidence interval.

	Screening	Day 32	Reduction Screening – Day 32	% reduction Screening – Day 32
Mean (SD)	47.3 (13.5)	46.3 (11.3)	1.0 (7.3)	0.4 (13.4)
95% Conf. Int.	38.6 – 55.9	39.1 – 53.4	-3.4 – 5.9	-8.1 – 8.9

Table 4. Type and degree of reported Adverse Events definitively, possibly or probably related to the treatment

Reported Adverse Events	**Degree classification**		
	Mild	**Moderate**	**Severe**
Abdominal dicomfort	1	1	0
Anorexia	1	0	0
Bilateral loin pain	0	1	0
Constipation	1	1	0
Deep venous thrombosis	0	0	1
Depression	1	0	0
Dysphagia	0	1	0
Headache	3	0	0
Heartburn	2	0	0
Insomnia	0	1	0
Low performance	1	0	0
Melena / hematemesis	0	0	1
Pain at injection site	1	0	0
Vomiting	2	0	0
Total	13	5	2

Discussion

In this trial, we examined metronomic BPC1 therapy in pre-treated metastatic PaC. After only 32 days of treatment, 75% of patients maintained stable disease while 25% had progressive disease. Quality of life improved significantly and observed toxicity was relatively mild.

Platinum-based anticancer drugs are important in many chemotherapy regimens. They exert their biological effects through DNA-binding by platinum and arrest of DNA replication [19]. However, the clinical value of platinum drugs is hampered by serious systemic toxicity and drug resistance, and a keen interest in functionalizing platinum complexes with, for example bioactive polymers, has arised. Functionalization means that the polymer is used for passively targeted platinum delivery.The purpose of functionalization is to improve the tumour selectivity or minimize the systemic toxicity of the drugs, to enhance the cellular accumulation of the drugs, to overcome tumour resistance to the drugs, to achieve a synergistic anticancer effect between different therapeutic modalities, or to add extra functionality to the drugs [20].

The platinum complex of the novel compound BPC1 is cis-diammineplatinum (II) dichloride in a low concentration. It is functionalized by a lignin-derived polymer of benzene polycarboxylic acids named BPCx-1. In BPC1 a polymer fraction with average molecular weight of 1500-2000 Da is associated with a single platinum atom [21]. BPCx-1 penetrates the cell membrane and into the cell nuclei where it transports metal ions, like platinum, across membranes [22]. In mice, Ehrlich tumour growth inhibition of a single platinum reactive moiety was highest for cisplatin, followed by BPC1 and finally carboplatin. However, the toxicity of BPC1 was considerably lower than that of carboplatin and especially cisplatin [21]. Besides platinum arrest of DNA replication the polymer BPCx-1 has its own pharmacological activity via immune modulation and induction of cytokine production [23], activation of pro-apoptotic genes and inhibition of oncogenes [24].

Metronomic chemotherapy is the protracted and dense administration of low dose chemotherapy with no prolonged drug-free intervals [25]. Angiogenesis is a hallmark of cancer and inhibition of angiogenesis is one of the primary mechanisms of action of metronomic therapy. Immune escape is another hallmark and low doses of chemotherapeutics, such as in metronomic therapy, has been shown to selectively kill immunosuppressive cell populations [26] and tilt the immune system from immunosuppression to immunostimulation [27]. The evidence from preclinical and clinical studies regarding the use of metronomic chemotherapy in pancreatic cancer has recently been reviewed by Romiti et al [28]. The few and mainly retrospective data from mixed study populations suggested good tolerability though mild activity of metronomic schedules. The authors concluded that maintenance therapy may be one of the most worthwhile developments for metronomic chemotherapy even in pancreatic cancer.

This is the first fully prospective trial to report on the combination of metronomic chemotherapy and a novel, functionalized platinum analogue in PaC. It is thus the first trial to allow for estimation of tolerability and influence on quality of life. The pre-treated metastatic patients of our trial were desperately ill, and since we had to anticipate difficulties by including patients with a sufficient expected survival time, we decided to go for a short-term trial but open for treatment beyond 32 days if some patients wanted it. Such a short treatment length is definitely a drawback and we could probably have continued treatment until progression, which is the standard. Despite this we found a very favourable toxicity profile and a significant improvement of QoL. With respect to treatment response according to RECIST criteria, we could hardly expect tumour regression after only 32 days. However, it is worth noting that mean Sum Lesions was almost precisely the same after 32 days of therapy, and to control tumour growth is actually the essence of metronomic treatment. In addition, 2 patients achieved a reduction in Sum Lesions of more than 20%, and mean Sum Lesions decreased substantially among 4 patients, who had a CT scan after another 28 days of treatment. It is an additional drawback that only 4 of 9 patients treated beyond day 32 had a follow-up CT scan but outside of protocol, incomplete follow-up of very ill patients is almost inevitable. Nevertheless, the findings indicate that metronomic BPC1 of longer duration may lead to tumour regression.

The metronomic therapy in our study was administered as an intramuscular injection as opposed to standard infusion therapy. We did not observe the common side effects of pancreatic cancer chemotherapy like neutropenia or fatigue, and only 2 patients had mild vomiting. Neither did we observe side effects in the blood biochemistry or haematology (data not shown). Though not consistently registered in our previous studies of breast cancer patients nor in the present trial, we learned that many patients preferred to have their injections at a local clinic on in their own home. It supports that metronomic BPC1 treatment is both patient-friendly and cost-effective for society.

In conclusion, findings from our prospective trial showed that short-term metronomic BPC1 chemotherapy controlled tumour growth, was safe and had a favourable effect on QoL. There is a need for more and randomized trials comparing long-term metronomic BPC1 treatment with guideline recommended chemotherapy in incurable PaC.

Research in Context

Evidence before this study

The treatment challenges with the rapidly increasing number of patients with incurable pancreatic cancer are recognized from all sides. First-line chemotherapy has prolonged survival to almost one year but only for the fit patients. Conventional chemotherapy is administered intravenously in maximum tolerated dose, many hospitals visits are necessary and even though reasonably efficient at first, at some point resistance or intolerable toxicity occurs. Treatment of cancer as a chronic disease is one of the time´s mantras and demands that the benefits of treatment for patients do not exceed the risks and disadvantages and that the organization of treatment and control can be handled cost-effectively for society. Metronomic chemotherapy is a treatment strategy directed against angiogenesis, acquired resistance to antineoplastic agents and immunosuppressive cell populations. The treatment principle is not new but no data from registered, prospective trials in a homogenous

population of pancreatic cancer patients were available at the time of initiation.

Added value of this study

Our prospective trial examined the outcome of metronomic therapy in the form of a daily intramuscular injection of a novel, functionalized platinum complex (BPC1) for pre-treated metastatic pancreatic cancer. The results of this small and short-time trial indicate that the treatment was safe, improved quality of life and could potentially suppress pancreatic cancer growth.

Implication of all the Available Evidence

Findings from this trial, as well as from previous (mainly retrospective) studies, support that metronomic chemotherapy is a safe alternative to standard treatment. However, the results of BPC1 treatment need to be validated in larger, randomized trials in a multicentre setting.

Abbreviations

AE: Adverse Events, ANVOA: Analysis of Variance, ASCO: American Society of Clinical Oncology, BPC1: A Novel Benzene-Poly-Carboxylic Acids Polymer with a Cis-Diammineplatinum (II) complex, CI: Confidence Interval, CT: Computed Tomography, CTC-NCI: Common Terminology Criteria for Adverse Events version 2.0 from National Cancer Institute, DNA: Deoxyribonucleic acid, EORTC: European Organization for Research and Treatment of Cancer, ESMO: European Society for Medical Oncology, IRB: Institution Review Board of the National Liver Institute, LOCF: Last Observation Carried Forward, MTD: Maximum Tolerated Dose, OS: Overall Survival, PaC: Pancreatic Cancer, QoL: Quality of Life Questionnaire, RECIST: Response Evaluation Criteria in Solid Tumors, SD: Standard Deviation, Sum Lesions: Sum of the Five Largest Target Lesions Diameters

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