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SECOND-LINE CHEMOTHERAPY WITH GEMCITABINE AND OXALIPLATIN IN COMBINATION WITH LOCO-REGIONAL HYPERTHERMIA (EHY-2000) IN PATIENTS WITH REFRACTORY METASTATIC PANCREATIC CANCER - PRELIMINARY RESULTS OF A PROSPECTIVE TRIAL*

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Abstract. There is no standard treatment for second-line in patients with metastatic pancreatic cancer. The treatment with local hyperthermia (41–42 °C) in order to enhance the activity gemcitabine-oxaliplatin on liver metastasis and primary advanced tumor was added as standard treatment. The primary objective was the response rate while the secondary objective were the safety of chemotherapy associated with hyperthermia and overall survival. There were 26 patients included, diagnosed with metastatic pancreatic cancer with progressive disease after gemcitabine treatment. The patients were enrolled in the period January 2005 – May 2011. The patients received gemcitabine 1000 mg/msq IV and oxaliplatin 100 mg/msq IV day 1 (GEMOX) combined with locoregional hyperthermia days1, 3 and 5 all repeated at 14 days. From 26 patients included, 19 patients had an evaluable response at the treatment. The toxicity of chemotherapy for these patients was related with chemotherapy (neutropenia grade III – 24%; anemia grade III – 8%, thrombopenia grade III – 6%; neurologic toxicity grade III – 22%. Toxicity related to hyperthermia was: discomfort because of bolus pressure (2%), pain related with position (12%), power related pain (2%). Rate of response was stable disease 53%, partial response 18% and progression disease 29%. Progression-free-survival was 3.9 months. Overall survival was 8.9 months.

Key words: metastatic pancreatic cancer, second-line chemotherapy, locoregional hyperthermia.

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1. INTRODUCTION

Pancreatic adenocarcinoma is the fifth leading cause of cancer - related death with almost 70 000 estimated deaths each year and predicted to become the fourth cause of cancer related death in both sexes in due course in the European Union [1, 2], as no chemotherapy combination has demonstrated statistical improvement in survival when compared to GEM alone. There is no firmly established standard chemotherapy [5] for patients refractory to first line chemotherapy with gemcitabine. Since the CONKO 003 trial published by Pelzer and colleagues [6] (showing that the combination of oxaliplatin and 5-Fu in the second-line setting for patients who failed gemcitabine revealed an OS of 4.8 months versus 2.3 months compared to best supportive care), one would consider a platinum-based regimen as adequate second-line therapy.

The clinical effectiveness of G and Cis or other platinum-based regimens has been shown so far in several clinical trials in the neoadjuvant, first-line and second-line setting [7–10].

In these conditions, the oxaliplatin-gemcitabine (GEMOX) protocol seems to be effective as second line chemotherapy of pancreatic cancer. Combination of hyperthermia and chemotherapy in pancreatic cancer was investigated in some studies and the results are promising [11].

Purpose and Rationale. In this trial we have as primary endpoint the response rate of combination chemotherapy (GEMOX) and locoreginal hyperthermia (oncothermia) for the patients with metastatic pancreatic cancer refractory at first line chemotherapy with gemcitabine.

The secondary objectives are: evaluation of safety for the combination chemotherapy-hyperthermia, evaluation of progression free survival and overall survival.

Patients and methods. Between january 2005 and may 2011, a total of 24 patients with metastatic pancreatic cancer with progressive disease after gemcitabine treatment were enrolled in the trial. The patients presented with pancreatic cancer of the head and tail, histologically proven. The main inclusion criteria was relapse of disease after gemcitabine treatment was confirmed (CT scan evaluation with RECIST 1.0.), and all patients signed a written informed consent form. The treatment protocol (gemcitabine-oxaliplatine plus locoregional hyperthermia) was approved by the Euroclinic Center of Oncology ethics committee.

Patients' characteristics. The main eligibility criteria for inclusion in the trial were: ECOG 0-2, adequate bone marrow, renal and hepatic function, no major cardiac diseases, no neurologic toxicities more than grade II (CTC-AE). The main characteristics of the patients are presented in Table 1.

Table 1

Characteristics of the patients

Characteristics	Enrolled patients (n=17)
Male	9
Female	8
ECOG Performance status	
ECOG 1	5
ECOG2	12
Stage at study entry	
Liver metastasis	6
Lung metastasis	4
Lymph node metastasis	6
Peritoneal carcinosis	4
Bone metastasis	6
Ascites/pleural effusion	8
Nr. of prior chemotherapy cycles (GEM) - median	5.4
Histopathologic types	
Duct cell carcinoma	11
Acinar cell carcinoma	1
Papillary mucinous carcinoma	2
Signet ring carcinoma	1
Adenosquamous carcinoma	1
Undifferentiated carcinoma	1
Prior regional therapy	
Surgery	6
Radiotherapy	3

The patients have previously received a median of five cycles of standard chemotherapy with gemcitabine as first line of palliative chemotherapy. Progression after gemcitabine treatment was established by CT scan measurements using RECIST system.

Chemotherapy regimen. The GEMOX protocol was administered to the patients (GEM 1,000 mg/m2 over 60 minutes day 1 and oxaliplatin 100 mg/m2 day 1 over 120 minutes every 14 days cycle). As antiemetic prophylaxy patients received a serotonin-5HT3-antagonist. Treatment modifications were mandated for myelosuppression or grade 3/4 toxicity. Oxaliplatin was held for patients with persistent grade 3 or 4 neuropathy or other oxaliplatin-related symptoms. Chemotherapy was reduced in the following cycle to 75% if nadir of granulocytes was below 1 g/L and platelets below 100 g/L or any non-haematological toxicity grade 3 occurred. After administration of four cycles a CT scan was performed and patients with progressive disease according to RECIST criteria went off treatment. Patients could withdraw or be removed from study at the discretion of the treating physician for unacceptable toxicity. Patients removed from study for any reason were observed for 4 weeks after the last dose of chemotherapy for toxicity assessment and until death for survival duration. Patients with stable disease, or

partial or complete remission were eligible to continue therapy on study until disease progression or intolerable toxicity occurred.

National Cancer Institute Common Toxicity Criteria (CTC-AE) version 2.0 was used during the study for toxicity reporting.

Locoregional hyperthermia. Regional hyperthermia was performed using the EHY-2000 device. This device functions on principles of electrohyperthermia (oncothermia). Oncothermia does more than simply warm deep layers of tissue - it also combines heat with a modulated electric field, with a carrier frequency of 13.56 MHz which is generated by two active electrodes. Oncothermic treatments were performed in combination with chemotherapy. The preheating phase consisted of slow adjustment of power from 70W up to a maximum of planned forward power (maximum 150W) over 10 min with a 60-min therapeutic time. Oncothermia aimed for tumour temperatures of 41-42.5 °C. It was applied on days 1, 3, 5 of every cycle. In day 1 the application was concomitant with GEM-OX infusion (Fig. 1). For patients with metastatic diseases the target area of hyperthermia was the largest metastasis or the area with the most metastasis (liver, lung, peritoneal carcinosis).

The patients were monitored during the oncothermia applications for adverse events and for vital signs (Blood pressure, heart rate, oximetry) at the beginning and at the end of the application.

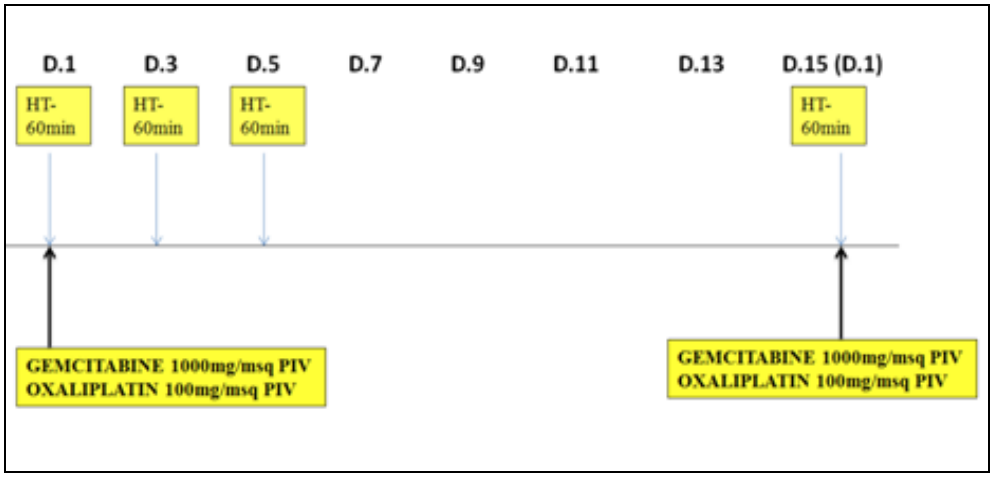

Fig. 1 – The treatment shedule of combination-chemotherapy (GEMOX) and oncothermia.

2. TOXICITY ASSESSMENT

Chemotherapy toxicity. Haematological and non-haematological toxicity were assessed according to Common Terminology Criteria for Adverse Events

(CTCAE) version 2.0. Febrile neutropenia was defined as fever of unknown origin without clinically or microbiologically documented infection with neutrophiles below 1.0 g/L and fever above 38.5 °C (Table 2).

Table 2

Toxicities observed with GEMOX + locoregional hyperthermia (NCI-CTCAE)

Parameter	Grade I	Grade II	Grade III	Grade IV
Hematologic toxicities (% of patients)	0	0	0	0
Anemia	12	10	8	0
Neutropenia	14	18	24	0
Thrombocytopenia	8	4	6	0
Non-hematologic toxicities (% of patients)	0	0	0	0
Nausea/vomiting	48	12	8	0
Peripheral sensory neuropathy	0	8	22	0
Creatinine elevation	0	6	12	0
Hyperthermia associated toxicities (% of all hyperthermic treatments)				
Power related pain	2	2	0	0
Position related pain	9	12	0	0
Bolus pressure	2	2	0	0

Hyperthermia-associated toxicity. Toxicity was analysed for acute and late hyperthermia-associated adverse events for each of a patient's hyperthermia treatment.

Evaluation of Treatment. Every patient was evaluated at the beginning of the study with CT scan. Response Evaluation Criteria in Solid Tumors were utilized for response assessment (CT scan) at 8-week intervals [12]. All responses had to be confirmed by repeat assessment at 4 weeks. Patients who had global deterioration of health status but without imaging evidence of disease progression were classified as symptomatic deterioration.

Statistical Methods. The Simon two-stage design was implemented for the primary objective of the study. The projected response rate for GEMOX chemotherapy is 15% (Poplin *et al*.). For the combination GEMOX + hiperthermia, the projected response rate is 18%. If there are < 2 Major responses (PR, CR), the study will be closed. If there are 3 or more major responses, the study will be extended to 37 patients.

The safety of combination chemotherapy-hyperthermia will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 2.0.

Progression free survival and overall survival are evaluated using Kaplan Meier survival curves. Overall survival was specified as time from first diagnosis until the date of death. Progression free survival was defined as time from the beginning of second treatment to progression of the disease.

3. RESULTS

Patient characteristics. Between January 2005 and May 2011, 24 patients with metastatic stage pancreatic cancer have received gemcitabine, oxaliplatin and deep locoregional hyperthermia as second-line therapy. First line therapy was gemcitabine alone and only the patients with progression disease after gemcitabine treatment were included in the study. All 24 patients were diagnosed with metastatic disease (proven to represent progressive disease). All patients had metastatic disease, altogether indicating a quite homogenous, but highly palliative patient population. Five patients were excluded (1 patient have performed surgical intervention, 3 patients had stopped the treatment after 1 cycle of GEMOX – according to patient's wish, 1 patient due to non-treatment-related death). Basic characteristics of the patients are shown in Table 1.

Treatment delivery and toxicities. A total of 19 patients have performed 234 chemotherapy cycles, with a median of 12.3 cycles/patient (range 5–18 cycles) and 229 hyperthermia treatments, with a median of 5 treatments/patient (range 5–17 cycles). Three patients have performed only 5 cycles due to progression of the disease and 2 patients have stopped the treatment according to patient's wish. Two patients required a dose reduction of Oxaliplatin due to neutropenia or peripheral neuroplathy (at one cycle and three cycles respectively), one patient required a dose reduction of Gemcitabine (for the reason of creatinine elevation), and four patients requiring both, due to neutropenia and gastrointestinal toxicities. All these toxicities were unrelated to hyperthermic treatments.

Six out of 229 hyperthermia sessions were stopped ahead of time. Reasons for premature break-up were back pain (one case), bolus pressure (one case), discomfort (two cases) and patient's wish (two cases).

The toxicities observed during treatment are provided in Table II. All patients were eligible for toxicity assessment. There was no grade 4 toxicity (according to NCI CTCAE guidelines, Table 2).

Response. Clinical response was evaluable in 19 of 27 patients. The results related with the response of the disease were the following: 9 patients (48%) had stable disease (SD), 4 patients (21%) had partial response (PR) and 6 patients (31%) had progressive disease (PD). Considering the Simon two-stage design with standard projected rate of GEMOX of 15% and combination (GEMOX + hyperthermia) projected rate of minimum 18%, the rate of response in the study of 21% is satisfactory to extend the trial to 37 patients.

Progression free-survival for the group of 19 patients treated in second line with GEMOX + hyperthermia was 3.9 months (Fig. 2). Overall survival for these patients was 8.9 months (CI 95% was 0.07402 - 0.5450, $P < 0.0001$).

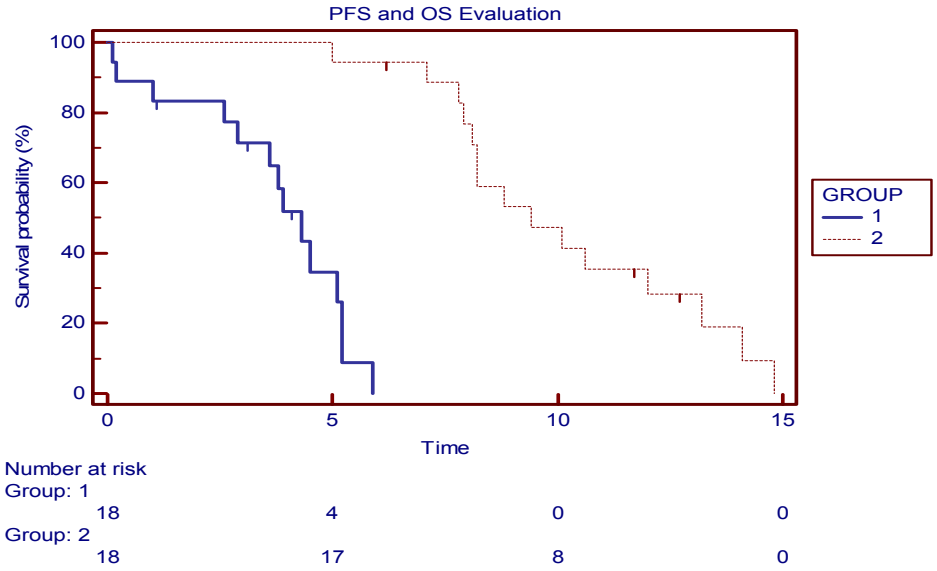

Fig. 2 – The PFS (group 1) and OS (group 2) of the patients.

4. DISCUSSION

Standard treatment in metastatic pancreatic cancer is represented by chemotherapy with gemcitabine in first line of treatment. Median progression free survival after gemcitabine chemotherapy is 3.3 months, ranging from 1.2–5.1 months [13–21].

Despite several efforts have been made to improve the outcome of advanced pancreatic cancer, the number of active compounds against pancreatic cancer is limited. Altogether new treatment options are needed for patients with advanced pancreatic cancer, specifically after failure of gemcitabine standard therapy. Gemcitabine and Oxaliplatin in combination with hyperthermia take advantage of the well-known additive effect of hyperthermia and represent an intensified treatment without adding the haematological toxicity of dose escalation or by adding a third chemotherapeutic compound. A few published reports on G and/ or Cisplatinum combined with hyperthermia in pancreatic cancer using different heat-inducing approaches such as whole body hyperthermia or intraoperative hyperthermia [22-24] also support the feasibility of combination of chemotherapy with gemcitabine and platinum compound and hyperthermia.

Concomitantly, the effects of hyperthermia in preclinical data demonstrated that hyperthermia supresses tumoral growth. Hyperthermia at 42.5°C produces changes in cell membrane and cytoskeleton, decreases hypoxia in tumor cells, influences the intracellular pH status [25]. Antioangiogenic effect of hyperthermia

is also manifested by increased production of PAI-I, direct cytotoxicity on proliferating endothelial cells and down-modulation on VEGF [26].

This type of hyperthermia generated by the EHY-2000 device (electro-hyperthermia at 13.56 MHz) also induces direct electromagnetic coupling on cancer cells and stimulates capacitively - coupled energy transfer which is absorbed primarily in extracellular space, causing depolarisation and water influx in cancer cells [27, 28].

In this trial, even in a small group an increase in response rate was proven, and the percentage of partial response is acceptable for future enrollment of more patients. The Simon two-stage design is an accepted statistical method in oncology for response evaluation and real data confirmation towards enrollment of more patients [29]. The other parameter (progression free survival) is acceptable for the second line therapy with GEMOX and hyperthermia (3.9 months) in comparison with other trials, where the median is 3.3 months. In this situation, a small benefit of hyperthermia on progression free survival can be taken into consideration.

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