

# Gemcitabine, cisplatin, fluorouracil and folinic acid as first line treatment of locally advanced and/or metastatic pancreatic cancer: a phase II study of the gruppo oncologico dell'Italia meridionale (G.O.I.M.)

## Research Article

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**Abbreviations:** PS, performance status; TGCR ,tumor growth control rate; PD, progressive disease; ORR overall response rate; OS, overall survival; TTP, time to disease progression; CB, clinical benefit; APca, advanced pancreatic cancer; SD, stable disease; OR, objective response; CR, complete response; GEM, gemcitabine; CDDP, cisplatin; 5-FU, 5-fluorouracil; FA, folinic acid; TXT, taxotere

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## Summary

A phase II trial was carried out to determine the activity of the triplet drugs combination of gemcitabine (GEM), cisplatin (CDDP) and 5-fluorouracil (5-FU) modulated by folinic acid (FA) in the treatment of advanced pancreatic cancer patients. The clinical benefit, the toxicity pattern, the median time to disease progression and the median overall survival were evaluated. Patients with measurable, locally advanced and/or metastatic pancreatic adenocarcinoma entered the trial. They received at the first cycle GEM at a dose of 1000 mg/m<sup>2</sup>, once a week for 7 consecutive weeks; CDDP was administered on day 1, 8, 15, 29, 36 and 42 at a dose of 25 mg/m<sup>2</sup> one hour before GEM, while FA/FU were given on the same day, immediately after GEM, at a dose of 100 mg/ m<sup>2</sup> and 300 mg/ m<sup>2</sup> bolus, respectively. After a 2-week rest, treatment was continued on day 1, 8, and 15 of a 4-week cycle; treatment was administered until progression or unacceptable toxicity. Thirty-three patients entered the trial. In the 28 patients evaluable for activity we obtained no complete response and 6 partial responses for an ORR rate of 21% (ITT analysis: 18%). Twelve stable disease (36%) and ten progressive disease (30%) were also observed. The median time to progression was 16 weeks and the median overall survival was 30 weeks. Twenty-two patients were evaluable for clinical benefit: 10 patients (40%) were considered as responders. The main grade 3-4 side effects (according to NCI criteria) were: thrombocytopenia 21%, neutropenia 18%, diarrhea and anemia 9%. Four patients discontinued treatment: 3 due to toxicity, 1 for refusal. The addition of 5-FU modulated by FA to the combination of GEM and CDDP does not seem to yield better results than the administration of the only GEM plus CDDP. The clinical benefit is similar to that observed in clinical trials employing GEM and CDDP alone, such as time to disease progression and overall survival. The toxicity pattern is severely increased by the addition of 5-FU/FA at least in this weekly schedule.

## I. Introduction

Cancer of the exocrine pancreas is considered one of the most difficult cancers to treat, since patients show a five-year overall survival rate lower than 5%. At the time

curative surgery with a median survival of 10-18 months while the majority of patients have locally advanced inoperable and/or metastatic disease with a median survival ranging from 3 to 6 months (Evans et al, 1997).

Single-agent gemcitabine (GEM) is currently

pancreatic cancer (APCa). Collective data gave employing only GEM have shown an objective overall response rate (ORR) in the range of 5.4-16.6% and a median survival of 3.9-6.3 months (Casper et al, 1994; Carmichael et al, 1996; Burris et al, 1997; Crino et al, 1997). In a randomised phase III trial, GEM obtained a statistically significant advantage in terms of clinical benefit (CB) rate, based on measurements of pain, functional impairment and weight loss (23.8% versus 5.4%,  $p:0.0022$ ), and overall survival (OS; 5.65 versus 4.41 weeks,  $p:0.0025$ ) when compared to the standard 5-fluorouracil (5-FU) (Burris et al, 1997). Combination chemotherapy with GEM, therefore, has been studied to improve the outcome of patients with APCa. 5-FU, the most extensively studied single drug in the treatment of APCa, yields an ORR of less than 10% with marginal impact on quality of life and OS (Ahlgren, 1996). In vitro the combination of 5-FU and GEM have demonstrated to have synergistic activity: GEM depletes the pools of cellular deoxyuridine monophosphate (dUMP) pools, decreasing competition with 5-FdUMP at the target enzyme thymidilate synthase: 5-FU metabolites may inhibit deoxycytidine monophosphate deaminase, the enzyme responsible for inactivation of GEM monophosphate (Kanzawa and Saijo, 1997).

Several phase I-II trials of GEM in combination with 5-FU have been conducted in patients with APCa. Although the dose and schedule of GEM were similar in all trials, the administration of 5-FU varied from protracted continuous infusion, to 24 hours continuous venous infusion (cvi), to weekly bolus at different dose levels, with or without folinic acid (FA). Four phase II trials evaluated the combination of GEM and bolus 5-FU administered for 3 consecutive weeks every 4 weeks. The ORR was in the range of 3.7-34.7% and the OS in the range of 4.4-9.0 months (Cascinu et al, 1998; Berlin et al, 2000; Murad et al, 2000; Pastorelli et al, 2000). Reported toxicities were mild, with a low percentage of hematological and gastrointestinal grade 3-4 side effects. Several other trials of GEM in combination with bolus or cvi 5-FU modulated by FA have been reported to date: the ORR was in the range of 5-26% and the median OS was 9 months (Gutzler et al, 1999; Hidalgo et al, 1999; Louvet et al, 1999; Kurtz et al, 2000; Lencioni et al, 2000; Polyzos et al, 2000; Rauch et al, 2001). Hematological and gastrointestinal side-effects were the main observed toxicities, whose severity depended on treatment schedule. However, in a recent phase III trial, the combination of GEM and 5-FU showed no advantage with respect to only GEM in median OS (6.7 vs 5.4 months,  $p:0.09$ ) and ORR (6.9 vs 5.6%) (Berlin et al, 2002).

Single-agent cisplatin (CDDP) has been reported to produce a 21% ORR in APCa patients with a median OS of 4 months (Wils et al, 1993). The combination of GEM and CDDP has been shown to be synergistic in vitro, since GEM is able to inhibit DNA repair after CDDP-induced damage, and CDDP is able to influence GEM catabolism through the inhibition of ribonucleotide-reductase (Bergman et al, 1996). Several schedules have been adopted for the combination of the two drugs. In two

plus CDDP on day 1 and 15 every 4 weeks, obtained a 11.5% and 26.0% ORR, a median time to progression (TTP) of 4.3 and 5.4 months, and a median OS of 8.2 and 7.1 months, respectively (Heinemann et al, 2000; Philip et al, 2001; Colucci et al, 2002). In a previous multicenter randomised phase III trial conducted by our group, the combination of GEM plus CDDP, administered weekly for 7 weeks, demonstrated to be more effective than GEM alone in terms of ORR (31% vs 10%,  $p:0.01$ ), and median TTP (20 vs 8 weeks,  $p: 0.048$ ) with a similar CB rate (52% vs 49%). The median OS showed a trend in favour of the combination arm but it did not reached the statistical significance (30 vs 20 weeks,  $p:0.48$ ). Toxicity recorded in the CDDP plus GEM arm was more acceptable than that reported in other phase II trials with the same combination (Heinemann et al, 2000). This difference most likely was related to dosages and schedules employed. A nationwide confirmatory phase III trial is currently ongoing.

Taking into account these data, the Gruppo Oncologico Italia Meridionale (GOIM) carried out a phase II trial with the aim to evaluate the activity of a triplet combination regimen in APCa patients. The main end-points of the study were the efficacy of the treatment in terms of ORR and CR rate, and the toxicity of the treatment; median TTP and OS were also evaluated.

## **II. Patients and methods**

### **A. Patient selection and study design**

Patients were enrolled into the study if they satisfied the following inclusion criteria: a) histological or cytological diagnosis of locally advanced and/or metastatic pancreatic carcinoma; b) bi-dimensionally measurable disease according to standard WHO criteria, c) no previous chemotherapy, hormonal therapy, or radiotherapy; d) age between 18 and 75 years; e) performance status (PS)  $\geq 50$  according to the Karnofsky Index; f) no evidence of congestive heart failure, serious arrhythmias or coronary artery disease; g) absence of severe uncontrolled metabolic, infectious or neurological disease; h) absence of other malignant neoplasms with the exception of adequately treated in situ carcinoma of the uterine cervix or non-melanotic skin cancer. Informed written consent was also requested from all patients before their inclusion into the study. Besides patients should have an adequate baseline bone marrow reserve (WBC count  $\geq 4,000/\text{mm}^3$ , neutrophils  $\geq 1,500/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$  and hemoglobin level  $\geq 10\text{gr/dl}$ ), an adequate hepatic function (levels of bilirubin and transaminases  $\leq 2.5$  normal values) and an adequate renal function (defined as serum creatinine concentration  $\leq 1.5\text{ mg/dL}$ , and BUN  $\leq 50\text{ mg/dL}$ ). Patients were excluded from the trial in the presence of brain metastases or any pre-existing medical condition of sufficient severity to prevent full compliance with the study. Geographical accessibility was also considered as a prerequisite in order to guarantee correct therapy and follow-up.

### **B. Treatment schedule**

Patients were centrally registered at the GOIM headquarters at the Oncology Institute of Bari, Italy. The treatment schedule was as follows: at the first cycle (8 weeks) GEM was administered as a 30-minute iv infusion at a dose of  $1000\text{ mg/m}^2$  diluted in 250 normal saline solution, once a week for 7 consecutive weeks; CDDP was administered on day 1 &

normal saline ensuring adequate hydration, one hour before the administration of GEM, while FA and 5-FU were administered on the same days, immediately after GEM, at a dose of 100 mg/m<sup>2</sup> in 500 cc of normal saline solution in 2 hours, and 300 mg/m<sup>2</sup> bolus, respectively. After a 2-week rest, treatment was continued on day 1, 8, and 15 of a 4-week cycle; treatment was administered until progression or unacceptable toxicity. Antiemetic therapy consisted of anti-HT3 agent and dexametasone. G-CSF was not administered routinely in this study.

Toxicities were graded according to the NCI common toxicity criteria. If multiple toxicities were observed, the dose administered was based on the most severe toxicity experienced. The dose adjustment schedule was evaluated at the beginning of a new administration. Dose reductions were performed as follows: if the absolute neutrophil count (ANC) was  $\geq 1,000/\text{mm}^3$  and platelets were  $\geq 100,000/\text{mm}^3$ , 100% of the dose was administered; if ANC was in the range of 500-1,000/mm<sup>3</sup> and platelets in the range of 50,000-100,000/mm<sup>3</sup>, 75% of the dose was administered; if ANC was  $<500/\text{mm}^3$  and platelets  $<50,000/\text{mm}^3$ , treatment was delayed for one week.

### C. Pre-treatment evaluation and follow-up

Staging and clinical evaluation procedures consisted of complete medical history and physical examination, EKG, complete peripheral blood cell counts, serum chemistry panel including serum tumor markers (CEA,Ca19-9). Bidimensionally measurable disease was determined by chest x-rays, CT and/or NMR as needed. Elevated CEA or Ca 19.9 levels were not considered as measurable disease. Endoscopy was employed according to patients' needs. After withdrawal from the study, patients underwent follow-up examinations every two months until death.

### D. Efficacy assessment

The first evaluation of disease status and CB was performed after the first cycle (8 weeks). Objective responses (OR) were determined according to the WHO criteria: a complete response (CR) was defined as the complete disappearance of all disease sites and of all disease-related symptoms with no evidence of new lesions for at least 4 consecutive weeks; a partial response (PR) was defined as a 50% or more reduction in the sum of the products of the longer perpendicular diameters of all measurable lesions, without any evidence of new lesions; stable disease (SD) was defined as a less than 50% reduction or a less than 25% increase in the sum of the products of the measurable lesions, with no evidence of new lesions; progressive disease (PD) was defined as a  $\geq 25\%$  increase in one or more lesions or the appearance of new lesions. The sum of CR, PR, and SD was reported as tumor growth control rate (TGCR). Patients with complete or partial response and those with stable disease continued treatment and were re-evaluated after two 28-day cycles. TTP was estimated from the date of first treatment to the first evidence of PD. OS was estimated from the date of first treatment to the date of death or the last follow-up.

Clinical Benefit (CB) assessment was based on the measurement of three common signs or symptoms two of which were defined as primary, i.e. pain and functional impairment, and one as secondary, i.e. weight loss. Pain was assessed by pain intensity and analgesic consumption. Pain intensity was determined daily by a visual analogic scale and the weekly value was defined as the median of the entire recorded daily values; an improvement of  $>50\%$  from baseline which was sustained for  $\geq 4$  weeks was considered to be a positive response.

baseline pain score of 30. Analgesic consumption was recorded weekly employing the following scale: 0 = no analgesic consumption; 1 = administration of non-steroidal anti-inflammatory drugs; 2 = consumption of codeine phosphate; 3 = oral administration of morphine sulfate; 4 = parenteral administration of morphine; 5 = neurosurgical procedures. A change from a higher to a lower level was considered to be a positive response. When consumption of analgesic drugs was considered within each level, patients who required an increase in their daily dose were defined as non-responders.

Functional impairment was assessed by the Karnofsky performance scale. Two different investigators determined baseline values weekly. For patients with a PS of 50, 60 and 70, an improvement of  $>20$  points from baseline which was sustained for  $\geq 4$  weeks was considered to be a positive response. Weight was measured weekly and a weight gain of  $>7\%$  (excluding third spaces) sustained for  $\geq 4$  weeks was considered to be a positive response. Therefore, a patient was classified as a clinical benefit responder if one of the two primary parameters improved without deterioration in the others or if the primary parameters were stable and a weight gain  $>7\%$  from baseline was observed.

### E. Statistical Analysis

Objective responses were reported as their relative rates with 95% confidence interval (95% CI) accordingly to an intent-to-treat (ITT) analysis and in evaluable patients. Percentages of response or other data were adjusted to the nearest unit. A univariate analysis of TTP and OS according to the Kaplan-Meier product limit estimate was performed. The population sample size was calculated considering a response rate of 20% in previous studies, assuming a minimum difference wished to be significant of 0.2 and estimated response rate of 30% with a type 1 error of 0.05 and a type 1 error of 80%. Therefore 33 patients had to be enrolled into the trial.

## III. Results

### A. Patients population and disease status

A total of 33 patients entered the trial; the main characteristics of the enrolled patients are summarized in **Table 1**. Overall, there were 20 males and 13 females with a median age of 65 years (range 42-75) and a median Karnofsky PS of 80 (range 50-100). Few patients (9%) had recurrent disease after radical surgery, while 30 patients (91%) had locally advanced and/or metastatic disease at the time of diagnosis; 22 patients (67%) had multiple sites of disease while 11 patients (33%) had only one site of disease. The main disease sites were primary tumor (30 patients), liver (15 patients), and lymph nodes (12 patients).

### B. Objective response, time to progression, and overall survival

Twenty-eight patients were available for objective response, while 4 patients withdrew from treatment, before re-evaluation: 3 patients due to treatment-related toxicity, and 1 because he refused treatment due to side-effects. ORR, CR rate, median TTP, and OS are depicted in **Table 2**. According to an ITT analysis, no CR and 6 PR were observed for an ORR of 18% (95% CL 7% - 35%), 12

patients (30%) had PD. In the evaluable patients the ORR was 21.4% (95% CL 8%-41%). The duration of objective responses were 12+, 28+, 32, 36, 48 and 52 weeks respectively (median 34 weeks), and were observed at primary tumor (20% of cases), liver (13%) and lymph nodes (17%). The median TTP was 16 weeks, while the median OS was 30 weeks. Thirteen patients (39%) were alive at 6 months and 5 patients (15%) at 1 year. The median survival of responder patients was 11 months.

**Table 1:** Patient characteristics

Enrolled:	33 (100%)
Sex	
Male:	20 (61%)
Female:	13 (39%)
Age (yr)	
Median:	65
Range:	42-75
Karnofsky PS:	
Median:	80
Range:	50-100
Stage	
III:	8 (24%)
IV:	25 (76%)
Surgery	
Radical:	3 (9%)
Biopsy:	30 (91%)
Sites of disease	
Pancreas:	30 (91%)
Liver:	15 (45%)
Lymph nodes:	12 (36%)
Other:	5 (15%)
Sites:	
Single:	11 (33%)
multiple:	22 (67%)

**Table 2:** Objective response rate, time to progression, overall survival

Enrolled patients:	33 (100%)
Evaluable patients:	28 ( 85%)
CR:	0 (00.0%)
PR:	6 (21.4%)
SD:	12 (36.3%)
PD:	10 (30.3%)
Overall response rate (ORR):	
Evaluable pts:	21.4%
ITT analysis:	18.0%
Median time to progression (weeks):	16
Median overall	

### C. Clinical benefit (CB)

Twenty-two (67%) of 33 patients enrolled were evaluable for CB assessment; 11 patients (50%) were evaluable for both PS and pain; 6 (18%) only for PS and 5 (15%) only for pain. Both pain and PS improved in one patient, whereas 4 patients showed a decrease in pain without deterioration of PS and 1 patient an improvement of PS with no change of pain. Furthermore 2 patients showed a weight increase > 7% with no change in PS and pain. Therefore 10 patients (40%; 95% CL 24%-68%) were considered CB responders. Improvement in the CB parameters was observed after the fourth week of administration (**Table 3**).

### D. Toxicity

The pattern of toxicity is depicted in **Table 4**. All patients were evaluable for toxicity. No toxic-related death has been observed. The main grade 3-4 toxicities were: neutropenia 18%, thrombocytopenia 21%, diarrhea 21%, anemia 9%, mucositis (12%), and nausea/emesis 2%. Four patients discontinued treatment for grade 3-4 thrombocytopenia and diarrhea. Grade 1-2 toxicity were: neutropenia 21%, thrombocytopenia 45%, anemia 30%, nausea/emesis 36%, diarrhea 12%, transaminases 15%, fever 12%, asthenia 12%, alopecia 18%.

**Table 3:** Results on Clinical Benefit

Evaluable patients:	22/33 (67%)
pain and performance:	11 (50%)
only performance:	6 (27%)
only pain:	5 (23%)
Responders:	
pain and performance:	3
only performance:	1
only pain:	4
weight:	2

**Table 4:** Toxicity recorded according to NCI criteria

<b>Mucositis</b>	--	2 (6)	4 (12)	--
<b>Diarrhea</b>	1 (3)	3 (9)	5 (18)	1 (3)
<b>Nausea/Vomiting</b>	8 (24)	4 (12)	1 (3)	--
<b>Leukopenia</b>	8 (24)	9 (27)	3 (9)	2 (6)
<b>Neutrophils</b>	4 (12)	3 (9)	3 (9)	3 (9)
<b>Anemia</b>	3 (9)	7 (21)	3 (9)	--
<b>Platelets</b>	6 (18)	9 (27)	4 (12)	3 (9)
<b>Transaminases</b>	3 (9)	2 (6)	--	--
<b>Asthenia</b>	4 (12)	--	--	--
<b>Loss of Hair</b>	4 (12)	3 (9)	--	--
<b>Flu-like syndrome</b>	2 (6)	1 (3)	--	--

## IV. Discussion

To date, GEM is considered as the standard palliative chemotherapy for patients with APCa by most oncologists on the basis of the results obtained in phase II-III trials reporting a CB response in 23-40% of patients. However GEM has limited antineoplastic activity when used as single-agent: the major objective responses are in the range of 5.4-16.6% with a median OS of 3.9-6.3 months. The Investigational New Drug Treatment Program reported a 12% ORR in 982 patients with APCa treated with single-agent GEM. The survival data from 2380 patients showed that the median survival was 4.8 months, with a 1-year survival rate of 15% (Storniolo et al, 1999). These data have led to numerous studies with the aim to evaluate the activity and efficacy of GEM employed in combination with other drugs that showed to be synergistic in vitro such as 5-FU, docetaxel, CDDP, and oxaliplatin. In this phase II study we have explored the activity and the tolerability of the triplet combination of GEM, CDDP and 5-FU/FA employing the same weekly schedule tested in our previous study aiming to maximize the potential synergism among the drugs and to reduce toxicity. In the twenty-eight evaluable patients we observed a 21% of ORR with a 36% of stable disease and a tumor growth control rate of 54%, a median TTP of 16 weeks and a median OS of 32 weeks. A CB was obtained in 40% of patients. These results are in the range reported for GEM-based combination chemotherapy regimens in medical literature, but they do not seem to be better than those observed in our previous randomised phase III trial with the combination of GEM and CDDP. With regard to toxicity, the addition of 5FU/FA to CDDP/GEM results in an increase in the severity of the side effects: we recorded grade 3-4 neutropenia in 18% of cases, diarrhea in 21%, anemia in 9%, mucositis in 12%, and thrombocytopenia in 21%. Toxicity determined the discontinuation of treatment in four patients (14%). Therefore the addition of 5-FU/FA to GEM/CDDP on a weekly schedule results in a significant increase in the severity and the incidence of toxicity without improving clinical efficacy.

Philip et al, (2001) considering the results of their previous phase II trial of GEM and CDDP, recently tested the activity and toxicity of the triplet combination of GEM administered at 1000 mg/m<sup>2</sup> on day 1, 8 and 15 of a 4-week cycle, CDDP at 50 mg/m<sup>2</sup> on days 1 and 15 and 5-FU 175 mg/m<sup>2</sup> cvi for 14 days obtaining analogue results than our trial (El-Rayes et al, 2003). Among the 47 evaluable patients they observed 11 PR (26%) and 27 SD (57%), with a median TTP of 5.7 months and a median OS of 8.6 months (El-Rayes et al, 2003). Also the main grade 3-4 toxicities were similar: neutropenia (19%), thrombocytopenia (38%) and mucositis/ stomatitis (15%).

GEM has also been tested in combination with docetaxel initially with poor results: less than 10% of ORR has been reported in three clinical experiences employing TXT at single administration every 3-4 weeks (Kakolyris et al, 1999; Cascinu et al, 1999; Clark et al, 2000). Different schedules of treatment have been explored; the weekly administration of both GEM and TXT seems to

Schneider et al, (2002) recently reported a 24.0% ORR employing GEM at the dosage of 750-1000 mg/m<sup>2</sup>/week and docetaxel at the dosage of 35 mg/m<sup>2</sup>/week for 3 weeks on a 4-week cycle. Recently the combination of GEM and CPT-11 revealed to be active with an ORR of 24%, a median TTP of 2.8 months and a median OS of 5.7 months in 45 patients with a low grade of grade 3-4 toxicities (Rocha-Lima et al, 2002). The GEM and oxaliplatin regimen was shown to yield 31% ORR, a median TTP of 5.3 months, and a median OS of 9.2 months and a CB of 40% in 64 eligible patients (Louvet et al, 2002).

In conclusion the data of this trial demonstrate that the triplet combination of GEM, CDDP and bolus 5-FU modulated by FA is an active treatment for patients affected by APCa. However the results achieved with our weekly schedule are no better than those observed in our previous randomised phase III trial with GEM plus CDDP (Colucci et al, 2002). Furthermore, the addition of 5-FU/FA seems to increase the severity of toxicity reported with weekly GEM/CDDP. Other schedules or combinations should be tested to increase the results in the treatment of APCa.

## References

- Ahlgren JD (1996) Chemotherapy for pancreatic carcinoma. **Cancer** 78, (suppl.1), 654-663.
- Bergman AM, Ruiz van Haperen VWT, Veerman G, Kuiper CM, Peters GJ (1996) Synergistic interaction between cisplatin and gemcitabine in vitro. **Clin Canc Res** 2, 521-530.
- Berlin DJ, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson A (2002) Phase III study of Gemcitabine in combination with Fluorouracil versus Gemcitabine alone in patients with advanced pancreatic carcinoma Eastern Cooperative Oncology Group Trial E 2297. **J Clin Oncol** 15, 3270-3275.
- Berlin JD, Adak K, Vaughn DJ, Flinker D, Blaszkowsky L, Harris JE, Benson III AB (2000) A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer an Eastern Cooperative Oncology Group Study (E3296). **Oncology** 58, 215-218.
- Burris III HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy K, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer a randomised trial. **J Clin Oncol** 15, 2403-2413.
- Carmichael J, Fink U, Russel RCG, Spittle MF, Harris AL, Spiessl G, Blatter J (1996) Phase II study of gemcitabine in patients with advanced pancreatic cancer. **Br J Cancer** 73, 101-105.
- Cascinu S, Silva RR, Barni S, Labianca R, Frontini L, Piazza E, Giordani P, Giuliodori L, Pessi MA, Fusco V, Luporini G, Cellerino G (1998) A combination of Gemcitabine and 5-Fluorouracil in advanced pancreatic cancer, a report from Group of the Studies of Digestive Tract Cancer (GISCAD). **Br J Cancer** 80, 1595-1598.
- Cascinu S, Gasparini G, Catalano V, Silva RR, Pancera G, Morabito A, Giordani P, Gattuso D, Catalano G (1999) A phase I-II study of gemcitabine and Docetaxel in advanced pancreatic cancer a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). **Ann Oncol** 10,

- Casper ES, Green MR, Kelsen DP, Heelan RT, Brown TD, Flombaum T (1994) Phase II trial of 2',2'-difluorodeoxycytidine in patients with adenocarcinoma of the pancreas. **Invest New Drugs** 12, 29-34.
- Clark JW, Ryan DP, Kulke MH (2000) Phase II study of gemcitabine and Docetaxel in patients with metastatic pancreatic cancer. **Proc. ASCO** 19, 1238.
- Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti p, Uomo G, Cigolari S, Testa A, Macello E, Lopez M (2002) Gemcitabine alone or with Cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma. A prospective randomized phase III study of the Gruppo Oncologico dell'Italia Meridionale. **Cancer** 4, 902-910.
- Crino L, Mosconi AM, Calandri C, Corgna E, Darwish S, Tonato M (1997) Gemcitabine in advanced pancreatic cancer a phase II trial. **Eur J Cancer** 33, (suppl.8)S280 (abst 1266).
- El-Rayes BF, Zalupski M, Shields A, Vaihampayan U, Heilbrun LK, Jain V, Adsay V, Day J, Philip PA (2003) Phase II study of gemcitabine, cisplatin and infusional 5-fluorouracil in advanced pancreatic cancer. **J Clin Oncol** 21, 2020-2925.
- Evans DB, Abbruzzese JL, Rich TR (1997) Cancer of the pancreas, in De Vita VT Jr, Hellman S, Rosenberg SA (eds) **Cancer Principles and Practice of Oncology**. (ed. 5). Philadelphia, PA, Lippincott, pp 1054-87.
- Gutzler F, Moehler M, Hosch WP, Wagner V, Hehme M, Rudi J, Stremmel W (1999) A phase I study of gemcitabine (GEM) in combination with five days 5-fluorouracil (5-FU) and folinic acid (FA) in patients with advanced adenocarcinoma of pancreas or bile duct. **Proc. ASCO** 18, A 1097.
- Heinemann V, Wilke H, Mergenthaler K, Clemens M, Konig HJ, Arning M, Schalhorn A, Possinger K, Fink U (2000) Gemcitabine and Cisplatin in the treatment of advanced and metastatic pancreatic cancer. Final results of a phase II study. **Ann Oncol** 11, 1399-1403.
- Hidalgo M, Castellano D, Paz-Ares L, Gravalos C, Diaz-Puente M, Alonso S, Cortes-Funes H (1999) Phase I-II study of Gemcitabine and Fluorouracil as a continuous infusion in patients with pancreatic cancer. **J Clin Oncol** 17, 585-92.
- Kakolyris S, Stathopoulos G, Tsavaris N, Androulakis N, Kouroussis C, Samantas E, Dimopoulos AM, Fountzilias G, Sarra E, Hatzidaki D, Samonis G, Georgoulas V (1999) First line treatment with docetaxel and gemcitabine in patients with a advanced pancreatic cancer a multicenter phase II study. **Proc ASCO** 18, 250a, (abst 960).
- Kanzawa F, Saijo N (1997) In vitro interaction between gemcitabine and other anticancer drugs using a novel three-dimensional model. **Sem Oncol** 24 (suppl.7), S7-8-S7-16.
- Kurtz JE, Kohser F, Negrier S, Trillet-Lenoir V, Walter S, Limach C, Unterreiner M, Kayitalire L, Jaeck D, Dufour P (2000) Gemcitabine and protracted 5-FU for advanced pancreatic cancer. A phase II study. **Hepatogastroenterology** 47, 1450-1453.
- Lencioni M, Falcone A, Masi L, Fioretto L, Meucci I, Di Marsico R, Pfanner E, Galli C, Bonifazi V, Mazzocchi B, Tognarini L, Conte PF (2000) Phase I-II study of Gemcitabine (GEM) in combination with 24 hours continuous infusion (CI) of 5-fluorouracil (5-FU) and L-leucovorin (LV) in patients (pts) with advanced pancreatic carcinoma (APC). **Proc. ASCO** 11(suppl. 4), A289.
- Louvet C, Hammel P, André T, Vanica R, Landi B, Balosso J, Cattani S, Fonck M, Flesch M, Colin P, Gruson T, deGramont A (1999) Multicenter phase II study in advanced adenocarcinoma patients with a combination of leucovorin, 5FU bolus and infusion, and gemcitabine (FOLFUGEM regimen). **Proc ASCO** 18, 275a, (abst.1054).
- Louvet C, André T, Uedo G, Hammel P, Bleiberg H, Bouleuc C, Gamelin E, Flesch M, Cvitkovic E, deGramont A (2002) Gemcitabine combined with Oxaliplatin in advanced pancreatic adenocarcinoma final results of a GERCOR multicenter phase II study. **J Clin Oncol** 20, 1512-1518.
- Murad AM, de Gusmao CBRA, Scalabrini-Neto AO (2000) Phase II trial of the use of gemcitabine and 5-fluorouracil (5-FU) in the treatment of advanced pancreatic (APC) and biliary tract (ABTC) adenocarcinoma. Final report. **Ann Oncol** 11 (suppl. 4), A 302P.
- Pastorelli D, Pedrazzoli S, Sperti C, Vicario G, Scelzi E, Santarossa S, Sgarbossa G, Fossier V, Manente P (2000) Phase II trial with gemcitabine (GEM) + 5-fluorouracil (5-FU) in advanced pancreatic cancer (APC). **Proc ASCO** 19, A 1110.
- Philip PA, Zalupski M, Vaitkevicius VK, Arlauskas P, Shields A (2001) Phase II study of Gemcitabine and Cisplatin in advanced or metastatic pancreatic cancer. **Cancer** 3, 569-577.
- Polyzos A, Tsavaris N, Kosmas C, Arnaoutis T, Vadiaka M, Apostolopoulos P, Vafiadis I, Tsatali K, Toskas A, Nikou G (2000) A phase II study of gemcitabine (GEM) plus 5-fluorouracil (5-FU) modulated by leucovorin (LV) for advanced pancreatic cancer. **Proc. ASCO** 19, A 1229.
- Rauch DP, Maurer CA, Aebi S, Pampallona S, Friess H, Ludwig C, Borner MM (2001) Activity of Gemcitabine and continuous infusion fluorouracil in advanced pancreatic cancer. **Oncology** 60, 43-48.
- Rocha-Lima CMS, Savarese D, Bruckner W, Dudek A, Eckardt J, Hainsworth J, Yunus F, Lester E, Miller W, Saville W, Elfring GL, Locker PK, Comptom LD, Miller LL, Green MR (2002) Irinotecan plus Gemcitabine induces both radiographic and Ca19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. **J Clin Oncol** 20, 1182-1191.
- Schmidt C, Fahlke J, Kettner E, Greiner L, Kuhn R, Eichelmann, Kroning H, Manger T, Ridwelski K, Lippert H (2002) Phase II multicenter study of gemcitabine and docetaxel in patients with inoperable or metastatic pancreatic cancer. **Proc ASCO** 21, part 1 577.
- Schneider BP, Ganjoo KN, Seitz DE, Picus J, Fata F, Stoner C, Calley C, Loeher PJ (2002) Phase II study of gemcitabine and docetaxel in combination for advanced pancreatic cancer- a Hoosier Oncology Group study. **Proc. ASCO** 21, part. 1 546.
- Storniolo AM, Enas NH, Brown CA, Voi M, Rothenberg ML, Schilsky R (1999) An investigational new drug treatment program for patients with gemcitabine. **Cancer** 85, 1261-1268.
- Wils JA, Kok T, Wagener DJT, Selleslags J, Duez N (1993) Activity of cisplatin in adenocarcinoma of the pancreas. **Eur J Cancer** 29, 203-204.



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