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*ORIGINAL ARTICLE*

# Phase II study of gemcitabine plus 5-fluorouracil biologically modulated by folinic acid plus long-acting formulation of octreotide (LAR) in patients with advanced pancreatic cancer

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## Summary

***Purpose:*** *To investigate the efficacy and toxicity of gemcitabine, in combination with 5-fluorouracil (5-FU) biologically modulated by folinic acid (FA) plus a somatostatin analogue (octreotide acetate-long acting formulation-LAR) that can both inhibit the action of several growth factors and angiogenesis, in patients with advanced pancreatic cancer.*

***Patients and methods:*** *Thirty-two patients with advanced symptomatic pancreatic cancer with measurable disease and median age 64 years (range 50-72) received the following combination: 5-FU, given at 350 mg/m$^2$ i.v. bolus, biologically modulated by FA 350 mg/m$^2$ on days 1, 2, 8 and 9; and gemcitabine, given by short i.v. infusion at 1000 mg/m$^2$ on days 1 and 8. The regimen was administered every 3 weeks. LAR 30 mg was given intramuscularly every 4 weeks.*

***Results:*** *Objective tumor response was documented in 7 out of 32 evaluable patients (all partial responses-PR), yielding a 22% response rate (RR) (95% CI 10.5-35). Sixteen (50%) patients (95% CI 31.4-60.8) remained with stable disease (SD), while 9 (28%) patients (95% CI 20.4-48.4) progressed while on chemotherapy. The median response duration (RD) was 7 months (range 4-18). The median time to tumor progression (TTP) was 7 months (range 2-20), while the median survival was 7 months (range 4-29). The probability of surviving beyond 12 months was 20%. Of the 32 patients with tumor-related symptoms who were considered evaluable for clinical benefit response, 25 (78%) had pain improvement, while 14 (44%) experienced weight gain during treatment. In general, performance status improved in 16 (50%) patients during treatment. Serum concentrations of Ca 19-9 were decreased by more than 50% in 14 (44%) of the 32 assessable patients. Chemotherapy was well tolerated with mild myelotoxicity. Gastrointestinal toxicity was moderate with mild mucositis.*

***Conclusion:*** *The combination of gemcitabine and 5-FU/FA plus LAR 30 was well tolerated and showed a moderate antitumor activity and a significant palliative effect on tumor-related symptoms. It would be interesting to evaluate in a randomized study the impact of octreotide administration on the palliative effect of the regimen.*

**Key words:** fluorouracil, folinic acid, gemcitabine, long acting octreotide, pancreatic cancer, phase II study

## Introduction

Advanced pancreatic carcinoma remains a lethal disease, mainly because of the advanced stage at diagnosis and the poor activity of chemotherapeutic agents. In addition, the impact of chemotherapy on patients' survival and quality of life is negligible. Of all chemotherapeutic agents, 5-FU has been studied most extensively using a variety of doses and modes of administration (i.e. combined with FA or as a continuous infusion) with RRs rarely exceeding 20%. The most important finding emerging from all these studies was

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that chemotherapy had a moderate effect on disease-related symptoms but survival has not been improved compared with best supportive care [1,2]. Other single agents and combination regimens failed to demonstrate additional benefit over single-agent 5-FU [3,4]. Therefore, 5-FU is considered one of the standard agents for palliative treatment of advanced pancreatic cancer.

Gemcitabine is a novel nucleoside analog with a wide spectrum of antitumor activity against a variety of solid tumors including pancreatic cancer. Gemcitabine was administered in a phase II study at doses of 800 to 1.250 mg/m$^2$ per week to 44 patients with advanced pancreatic cancer. An objective RR of 11% was documented but, most importantly, improvements in disease-related symptoms were reported not only in responding patients, but also in those that their disease remained stable [5]. In a recently published randomized trial, gemcitabine was shown to be more effective than 5-FU in terms of objective tumor RRs and improvement of clinical benefit with a small survival advantage [6]. Therefore, gemcitabine has become the new standard agent for advanced pancreatic carcinoma. A prior study evaluated the efficacy of gemcitabine in patients with pancreatic cancer that failed treatment with 5-FU. The reported clinical benefit RR of 27% suggested lack of cross-resistance between the two aforementioned agents [7]. In addition, the combination of the two agents has a theoretical rationale, based on their common mechanism of action; blocking of pyrimidine nucleotide synthesis and targeting of different metabolic pathways [8]. The results of preclinical studies in conjuction with the reports of clinical trials where gemcitabine and 5-FU can be safely administered using different schedules of administration [9,10] provide a clear rationale for a phase II study where the two standard agents can be combined. In the present phase II study we evaluated the efficacy of combining gemcitabine with 5-FU biochemically modulated by FA and the long-acting formulation of octreotide acetate 30 mg (LAR 30) in patients with advanced adenocarcinoma of the pancreas. The applied doses of gemcitabine and 5-FU have been decided, based on the reports of several feasibility phase I-II trials [9-11]. In the present study, gemcitabine was given at 1000 mg/m$^2$ on days 1 and 8 every 3 weeks, while 5-FU-FA were administered one hour later on the same day as well as on the following day, in order to develop the conditions for potential drug synergism. In addition, experimental data suggest that somatostatin analogues might exert an antitumor effect through a number of different mechanisms. Somatostatin analogues were found to inhibit IGF-1, TGF-β and EGF, agents responsible to stimulate tumor growth. Somatostatin analogues can also inhibit angiogenesis, while they exert a direct antiproliferative effect on certain tumor cells [12,13]. It is interesting to note that the action of octreotide is not directly correlated to its binding affinity to the somatostatin receptors [14]. Somatostatin analogues were administered in prior studies in patients with disseminated pancreatic tumors where the tolerability of treatment was documented. Although objective responses have never been reported in patients with pancreatic cancer, recently it has become more evident that symptomatic palliation rates may exceed sometimes the objective response rates [14,15]. The dose of LAR 30 is somewhat empirical, and is based on information derived from its effectiveness in inducing palliative effects in neuroendocrine tumors.

The objective of this study was to evaluate the efficacy and toxicity of the combination and estimate any improvement in cancer-related symptoms as well as in performance status of patients suffering from this debilitating disease.

## Patients and methods

### *Patient selection*

Patients with histologically or cytologically confirmed pancreatic adenocarcinoma with locally advanced, unresectable or metastatic disease were eligible for the study. Other eligibility criteria included the following: bidimensionally measurable disease, age between 18 and 75 years, a WHO performance status of 0 to 2, no prior chemotherapy or radiotherapy, a life expectancy at least 3 months, absence of biliary tract obstruction, and adequate bone marrow function (white blood cell [WBC] ≥4.000/μL, absolute neutrophil count [ANC] ≥1.500/μL and platelet count ≥100.000/μL). Normal renal (serum creatinine concentration <1.5 mg/dL) and liver (total serum bilirubin concentration ≤ 2 mg/dL and transaminase levels ≤ 3 times the upper normal limit [for patients with liver metastastes ≤ 5 times]) function tests. Patients with central nervous system (CNS) involvement were excluded from the trial. Prior surgery was allowed, but at least 4 weeks must had passed since the date of procedure. Patients with overt infections or any pre-existing medical condition of sufficient severity to prevent full compliance with the study were excluded. All patients gave written informed consent.

### *Treatment schedule*

All patients were treated on an outpatient basis. The dose of gemcitabine was 1000 mg/m$^2$ and was ad-

ministered by short i.v. infusion on days 1 and 8. 5-FU was administered as an i.v. bolus at 350 mg/m$^2$ on days 1, 2, 8 and 9. On the same days, FA 350 mg/m$^2$ was administered 1 h prior to 5-FU. Antiemetic treatment with ondansetron 8 mg i.v. prior to gemcitabine was administered on days 1 and 8. Cycles were repeated every 21 days. In addition, LAR 30 was administered intramuscularly every 4 weeks.

*Dose modification*

Treatment was continued until disease progression. Responding patients could continue to receive treatment until the appearance of PD or the development of serious toxicity. Treatment was delayed or omitted, if ANC was less than 500/μL or if the platelet count was less than 50.000/μL. Recombinant human G-CSF was administered in case of severe neutropenia at 150 μg/m$^2$/day for 5-10 days or as required. The doses of gemcitabine were reduced by 25% if the ANC was between 500 and 1.000/μL or the platelet count was between 50.000 and 100.000/μL. If a patient developed diarrhea or mucositis of grade 1-2, the dose of 5-FU was not reduced. If gastrointestinal toxicity was more severe, the dose of 5-FU was reduced by 20%. Toxicities were graded according to the WHO guidelines [16].

*Pretreatment and follow-up studies*

Before entry onto the study, the disease state of each patient was evaluated by full medical history, physical examination, performance status, analgesic requirements and disease-related symptoms via quality of life (QoL) measurement that included pain, performance status and weight loss according to prior studies [6]. Other pretreatment evaluation included complete blood count with differentials and platelet counts, standard biochemical profile, serum carcinoembryonic antigen (CEA) and Ca-19-9 determinations, chest-x-rays, computed tomography scans of the chest, upper and lower abdomen, and electrocardiogram. During treatment, complete blood count with differentials and platelet counts were performed weekly. Before each course of treatment, a full medical history was taken and physical examination performed. Biochemical tests, CEA, Ca-19-9 determinations and chest-x-ray were performed every 3 weeks. Tumor assessments by physical examination and computed tomography scan were evaluated every 2-3 courses.

*Definition of response*

Tumor assessments were evaluated using standard WHO criteria. Complete response (CR) was defined as the disappearance of all measurable and assessable disease at all sites for a minimum of 4 weeks. PR was defined as ≥ 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions for a minimum of 4 weeks with no appearance of new lesions. SD was defined as a decrease of total tumor size < 50% or an increase < 25%. Progressive disease (PD) was defined as an increase in the sum of the products of the diameters of measurable lesions by ≥ 25% or a clear worsening of any lesions that had previously disappeared, or the appearance of a new lesion(s).

*Assessment of clinical benefit*

The evaluation of clinical benefit in symptomatic patients was based on both physicians' observation and patients' own evaluation of symptoms using the criteria previously developed in the evaluation of gemcitabine in pancreatic cancer; these are: pain, performance status and weight as reported by Burris et al. [6]. A > 50% decrease in analgesics consumption with no need for narcotics in association with patients' own evaluation of a 50% decrease of pain on a Memorial Pain Assessment Card (MPAC) 0-100 visual analogue scale was characterized as pain improvement. If patients estimated a 50% increase in pain intensity while a 50% increase of consumption of analgesic was documented, then pain deterioration was clear. All other cases were characterized as "no change". Performance status was assessed weekly by two independent observers. Disease status was estimated every 4 weeks. Weight change was considered a secondary measure. Patients were classified as either positive, stable, or negative for each of the 3 clinical benefit measures. In all cases, positive indicated a sustained (≥ 4 weeks) improvement over baseline. For patients to achieve an overall rating of positive response they had to be positive for at least one parameter without worsening of any other parameter for at least 4 weeks. If pain and performance status were estimated stable then the patient was classified as having achieved a response only if weight was positive. All other patients were classified as not having achieved clinical benefit response [6].

*Statistical methods*

According to Simon's two-stage minimax design [17], a sample of 40 patients has approximately 80% power to accept the hypothesis that the true RR is >30%, while 5% significance to reject the hypothesis

that the true RR is < 20%, if less than 8 responses occur. At the first stage, if less than 5 responses occur out of the first 21 patients, the study will conclude that the anticipated RR is < 20% and will terminate. Thereby, the probability of accepting a therapy with a real RR < 20% and the risk of rejecting a treatment with a RR > 30% would be in both cases < 10%. RD was calculated from the day of the documentation of response until disease progression. TTP was estimated from study entry until disease progression and overall survival was measured from study entry until death. For RRs, 95% confidence intervals were calculated [18]. Actuarial probability of survival and median TTP were estimated by the Kaplan-Meier product limit method [19].

## Results

### *Patient population*

Between May 2000 and May 2002 a total of 32 chemonaïve patients (20 men and 12 women with a median age of 64 years) were enrolled. All patients were evaluable for response and toxicity. Patient characteristics at entry are summarised in Table 1. The majority of patients (88%) had metastases in the liver, while 81% had a tumor mass in the pancreatic area and 44% regional lymph node involvement. Two patients had undergone Whipple's operation with disease recurrence after a median of 12 months (range 8-24). Fourteen (44%) patients had undergone palliative surgery for biliary and/or gastrointestinal decompression, while 16 (50%) patients had received endoscopic stents for relieving obstructive jaundice before study entry. All patients were suffering from disease-related symptoms. All 32 symptomatic patients had pain at study entry, requiring more than 10 morphine-equivalent mg/day for pain control. Similarly, 25 (78%) patients had weight loss, all patients (100%) had asthenia, 16 (50%) had vomiting, 16 (50%) had diarrhea and all (100%) patients had anorexia.

**Table 1.** Patient characteristics (n=32)

| *Characteristic* | *No. of patients* | *%* |
|---|---|---|
| Age, years | | |
| Median | 64 | |
| Range | 50-72 | |
| Male/Female | 20/12 | |
| Performance status | | |
| 0 | 6 | 19 |
| 1 | 20 | 62 |
| 2 | 6 | 19 |
| Prior surgery | | |
| Whipple | 2 | 6 |
| Palliative bypass | 14 | 44 |
| Stent only | 16 | 50 |
| Sites of disease | | |
| Pancreas | 26 | 81 |
| Lymph nodes | 14 | 44 |
| Peritoneum | 4 | 13 |
| Liver | 28 | 88 |
| Other | 6 | 19 |

### *Compliance with treatment*

A total of 207 chemotherapy courses were administered. The median number of cycles per patient was 6 (range 2-18) and the median interval between cycles was 21 days (range 21-30). Twenty (7%) cycles were delayed because of patients' requests for reasons unrelated to disease or to treatment. Ten (3%) cycles were delayed because of non neutropenic infectious complications, mostly cholangiitis.

### *Objective response and survival*

Response rates, RD, TTP and survival data are summarized in Table 2. There were 7 PRs, yielding a RR of 22% (95% CI 10.5-35). Sixteen (50%) patients had SD (95% CI 31.4-60.8), while 9 (28%) patients progressed while on chemotherapy (95% CI 20.4-48.4). The median RD was 7 months (range 4-18), while the median time to achieve a response was 3 months (range 2-4). The median TTP for the 23 PR and SD patients was 6 months (range 2-20). The median duration of SD was 3 months (range 2-8) The median overall survival of the whole group was 7 months (range 4-29), while the probability of surviving beyond 12 months was 20%.

**Table 2.** Summary of treatment results (n=32)

| *Therapeutic outcome* | | *No. of patients* | *%* | *95% CI* |
|---|---|---|---|---|
| Complete response | | – | – | – |
| Partial response | | 7 | 22 | 10.5-35 |
| Stable disease | | 16 | 50 | 31.4-60.8 |
| Progressive disease | | 9 | 28 | 20.5-48.4 |
| Response duration (mos) | Median 7 | | | |
| | Range 4-18 | | | |
| Time to progression (mos) | Median 7 | | | |
| | Range 4-18 | | | |
| Overall survival (mos) | Median 7 | | | |
| | Range 4-29 | | | |

*Clinical benefit response*

Clinical benefit response data are summarised in Table 3. Thirty-two patients with tumor-related symptoms (pain, performance status and weight loss) were considered evaluable for clinical benefit response. In 25 of 32 patients (78%), pain intensity and analgesic consumption was reduced by more than 50% as compared with baseline values. Five (16%) patients were classified as no change, while only 2 (6%) patients experienced pain aggravation. In half of the patients with pain improvement, the analgesics were totally discontinued, usually by the completion of the second course. Performance status improved in 16 (50%) patients during treatment: in 7 (22%) patients performance status remained unchanged and in 9 (28%) non-responding patients performance status deteriorated. Weight loss was reported by all 32 patients at study entry: 9 (28%) of these patients experienced an increase in their weight, in 16 (50%) of these the weight remained unchanged, while in 7 (22%) their weight decreased. Body weight was not associated with edema or ascites in any patient. The median time to achieve a clinical benefit response was 2 months (range 1-3), while the median response duration of clinical benefit was 7 months (range 5-7). The compliance rate was very high (>85%).

*Other measures of efficacy*

Among the 32 patients who presented with elevated levels of Ca19-9, a decrease of the marker was noted in 16 (50%) of them: in 14 (44%) patients the decrease of serum Ca-19-9 concentration ranged from 50 to 100%. In the remaining patients, Ca-19-9 concentration was either unchanged or increased progressively.

*Toxicity*

All patients were assessable for toxicity (Table 4). Hematologic toxicity was mild. Grade 2 leukopenia and granulocytopenia were observed in 6 (19%) and 4 (12%) patients, respectively. Grade 2 thrombocytopenia was noted in 4 (12%) patients, while grade 2 and 3 anemia was observed in 20 (62%) and 4 (12%) patients, respectively. Anemia most probably was related to chronic disease than myelotoxicity, and responded to erythropoietin administration. The most frequent side effect of chemotherapy was mucositis, with 16 (50%) patients experiencing grade 2 and 4 (12%) grade 3 toxicity. Non-neutropenic infection (cholangiitis) developed in 6 (19%) patients due to prior operations or prior stent placement. All episodes were well controlled with i.v. antibiotics, while patients who manifested at least two episodes were placed on oral antibiotics as chemoprophylaxis with cephalosporines alternating with kinolones every week.

**Table 4.** Summary of maximum treatment-associated toxicity (n=32)

| *Toxicity** | *Grade 2 Patients, n* | *%* | *Grade 3 Patients, n* | *%* |
|---|---|---|---|---|
| Leukopenia | 6 | 19 | – | – |
| Granulocytopenia | 4 | 12 | – | – |
| Thrombocytopenia | 4 | 12 | – | – |
| Anaemia | 20 | 62 | 4 | 12 |
| Symptomatic toxicity | | | | |
| Nausea/vomiting | 6 | 19 | – | – |
| Mucositis | 16 | 50 | 4 | 12 |
| Diarrhea | 6 | 19 | – | – |
| Constipation | 4 | 12 | – | – |
| Infection | 6 | 19 | – | – |
| Alopecia | 16 | 50 | | |
| Cutaneous | 6 | 19 | 4 | 12 |

*No grade 4 toxicity was encountered

## Discussion

In the present study, we evaluated the feasibility and efficacy of gemcitabine plus 5-FU/FA administered every 3 weeks in combination with long-acting octreotide in patients with advanced pancreatic carcinoma. Gemcitabine is considered standard agent for pancreatic cancer, although its impact on patient survival -with median values ranging from 4.8 to 5.6

**Table 3.** Results of clinical benefit response (n=32)

| | *Improvement* | | *No change* | | *Deterioration* | |
|---|---|---|---|---|---|---|
| *Parameters* | *No. of patients* | *%* | *No. of patients* | *%* | *No. of patients* | *%* |
| Pain | 25 | 78 | 5 | 16 | 2 | 6 |
| Performance status | 16 | 50 | 7 | 22 | 9 | 28 |
| Weight | 9 | 28 | 16 | 50 | 7 | 22 |

months- is not very significant [6,20]. 5-FU modulated by FA was chosen as the second agent because of its consistent activity in pancreatic cancer and its non cross-resistance to gemcitabine, as previously reported in clinical trials [7].

The addition of octreotide as a third agent was decided, based on several reports on its inhibitory effect on experimental pancreatic cancer [21,22], as well as on its favorable effect in patients with cancer of the pancreas in terms of subjective improvement and "sharp increase in performance status" [22]. The effectiveness of octreotide in pancreatic cancer has also been evaluated in several randomized studies. In two of them it was compared to placebo [23,24] and in one it was compared to 5-FU [25]. In none of these trials octreotide administration had any benefit in survival. However, in a fourth randomized study, octreotide administration had a significant impact on survival, achieving a median survival of 20 weeks as compared to 11 weeks of the control group [26]. In addition, in a recent phase II study, high-dose octreotide (3×2000 μg per day) was administered subcutaneously in 49 patients with pancreatic cancer. Although no objective responses were reported, octreotide treatment resulted in SD in 20% of the patients for more than 12 weeks. The reported median progression-free survival and the median survival for the group were 9.0 and 21 weeks, respectively [27]. With respect to clinical benefit response, there were no major changes between baseline treatment period and the end of study [27]. The authors of the aforementioned study had proposed a phase II study where chemotherapy and octreotide should be combined, so that any possible synergistic effect could be observed. As shown in our study, the combination of chemotherapy plus octreotide yielded a 22% objective RR and a high clinical benefit response (> 50%). The median RD was 7 months, but many patients remained in remission for 12-18 months. The median TTP for 23 patients was 7 months. It is interesting to note that 50% of patients had SD for at least 3 months, while 8 patients with SD survived for 10 months after the start of chemotherapy. The median overall survival of the group was 7 months. We believe that the apparent prolongation of patients' survival was significant, considering the high proportion of patients with liver metastasis (88%) as opposed to other studies that involved patients with predominantly locoregional disease, for which it is known to carry a much better prognosis. In the Spanish study, where gemcitabine was combined with continuous infusion of 5-FU, the reported RR was 19% and the median survival was 10.3 months, but the proportion of patients with liver metastasis was 46% [10]. In a study from Austria, single-agent high-dose gemcitabine was administered to patients with pancreatic cancer, with myelotoxicity being the commonest side effect. The reported RR was 21% and the median survival 8.8 months, but the proportion of patients with liver metastasis was 58% [28]. The present study evaluated also the clinical benefit response as a composite measure of pain, analgesic consumption, weight gain and improvement of performance status. Cancer-related pain was improved in 78%, while 28% of the patients gained weight. Overall, performance status was improved in more than 50% of the patients. Serum concentration of Ca-19-9 decreased by at least 50% in more than 30% of the patients. These observations strongly suggest that treatment of pancreatic carcinoma with the 3 agents as applied in the present study may result in a significant clinical benefit response.

In medical literature, combinations of gemcitabine and 5-FU, either bolus or in continuous infusion, indicate that a significant proportion of patients (> 50%) with pancreatic cancer achieve a clinical benefit response [11,12]. In several studies, as well as in the present study, a significant proportion of patients who attained a clinical benefit response did not achieve an objective tumor response as determined by radiographic tumor assessment. Such discrepancies between objective tumor response and clinical benefit have been reported in several trials, in which patients with pancreatic cancer have been treated with a gemcitabine-containing regimen [9,13]. It is possible that the addition of 5-FU/FA and octreotide had an enhancing effect on the favorable activity of gemcitabine without any further increase in side effects. However, in a recent large randomized study of the Eastern Cooperative Onclology Group (ECOG) the combination of gemcitabine plus 5-FU in patients with advanced pancreatic cancer was not superior to single-arm gemcitabine in terms of median survival: 6.7 months for the combination *versus* 5.4 months of the single agent [29]. However, current data indicate that other gemcitabine-5-FU combinations might provide a therapeutic advantage over single-agent gemcitabine. Several studies have been published before the completion of our study [30,31]. Weekly gemcitabine-5-FU-FA yielded a 21% RR, similar to our results, and a 1-year survival of 36% in a study from Argentina [30]. Also, in a French study, the bimonthly administration of the 3 agents yielded a 26% RR with 32% of patients achieving 1-year survival [31]. Other more recent studies were published after the results of the ECOG study were released and indicate that a different mode of 5-FU administration as compared with the ECOG study might yield higher RRs. Biweekly administration of gemcitabine-5-FU and FA (with 5-FU-FA given for 3 days) achieved a

RR close to 30%, with a 13.1-month median survival [32]. Another phase I-II study published recently, also indicated that weekly gemcitabine and 24-h infusion of 5-FU might achieve a high clinical benefit response and an actuarial 1-year survival rate of 33% [33].

A review of recently completed and ongoing clinical trials of a gemcitabine-5-FU combination was published in 2002. In these trials, 5-FU administration varied widely from bolus to protracted infusion over several weeks. The authors could not draw definitive conclusions, mainly because the majority of these studies represented phase I and II study results. Although they were aware of the results derived from the ECOG phase III study, they concluded that another gemcitabine-5-FU combination might provide a therapeutic advantage over single-agent gemcitabine [34].

The toxicity profile of the present regimen was relatively mild. Indeed, 50% of the patients developed grade 2, and 12% grade 3 mucositis as a result of 5FU-FA administration for 4 days every 3 weeks. Leukopenia and thrombocytopenia were mild with 19% and 12% of patients, respectively, developing grade 2 toxicity. Similarly, 19% and 12% of patients developed grade 2 and 3 cutaneous toxicity, respectively. Six patients developed non-neutropenic febrile episodes as a result of prior intra-abdominal anastomoses and were successfully treated with i.v. and/or oral antibiotics.

Gemcitabine combinations with other agents, such as cisplatin, irinotecan, matrix metalloproteinase inhibitors or farnesyltransferase inhibitors, in phase III studies failed to show a significant survival benefit for the combination. In addition, their toxicity, as compared with the toxicity induced by gemcitabine-5-FU combinations, was significantly greater [35-37]. Therefore, 5-FU remains the low-toxicity combination partner for gemcitabine.

In conclusion, the described triple-agent regimen seems to be an effective palliative treatment for patients with advanced pancreatic carcinoma, and is associated with a low toxicity profile. Considering the inability to discern whether the favorable results are attributable to the use of octreotide, it would be very interesting to evaluate its effect on tumor growth in a randomized study with chemotherapy in both arms and octreotide added in one of the treatment arms.

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