FOLFOX-6 Combination as the First-Line Treatment of Locally Advanced and/or Metastatic Pancreatic Cancer

Marwan Ghosn, MD, Fadi Farhat, MD,† Joseph Kattan, MD,* Fariha Younes, Pharm D,* Walid Moukadem, MD,‡ Fadi Nasr, MD,* and Georges Chahine, MD**

Objective: Advanced pancreatic carcinoma (APC) has a poor prognosis and chemotherapy remains the most common approach. Gemcitabine was the only drug recently approved for use as single agent therapy in APC. However, the combination of oxaliplatin and 5-fluorouracil (5-FU) has shown some promising results. This phase II trial was conducted to investigate the efficacy of oxaliplatin, 5-FU, and folinic acid (FOLFOX-6) in previously untreated APC patients.

Methods: We studied response rate, time to progression, and toxicity profile. Treatment included oxaliplatin 100 mg/m^2 and folinic acid 400 mg/m^2 on day 1 followed by a 5-FU bolus 400 mg/m^2 and a 46-hour infusion of 3000 mg/m^2 every 2 weeks.

Results: From January 2003 through December 2004, 30 eligible patients were included. Median age was 65 (range, 38–75). There were 22 patients who had metastatic disease and 29 had an adenocarcinoma. A total of 181 cycles were delivered with a mean of 6 cycles per patient. There were 23 patients evaluable for response. There were 8 patients with partial response (27.6% response rate) and 10 with stable disease status (34.5%), while tumor growth control was found in 62% of the patients. Recorded toxicities of grade 3/4 were: neutropenia (26.67%), thrombocytopenia and anemia (10% each), diarrhea (6.67%), and mucositis (3.33%). Neurosensory toxicity was mild. The median time to progression and the median survival were 4 and 7.5 months, respectively.

Conclusion: In patients with APC, FOLFOX-6 regimen achieved an interesting response rate within a tolerable level of toxicity. This regimen seems to warrant further controlled investigation to confirm its efficacy.

From the *Hotel-Dieu de France University Hospital, Beirut, Lebanon; †Hammoud Hospital, Sidon, Lebanon; and ‡Haikal Hospital, Tripoli, Lebanon; for the Cancer Research Group/Collaborative Group, Beirut, Lebanon (Protocol CRG/CG PA 011).

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Reprints: Marwan Ghosn, MD, Professor and Chairman, Department of Hematology–Oncology, Hôtel-Dieu de France University Hospital, Achrafieh, Blvd Alfred Naccache, P.O. Box 166830, Beirut, Lebanon. E-mail: drghosn@sodetel.net.lb.

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Cancer of the pancreas continues to be a serious health problem with approximately 227,000 deaths per year in the world mainly because of late presentation. Ninety percent of cases approximately are diagnosed with advanced pancreatic carcinoma at the time of diagnosis. Deaths are associated with the aggressiveness of pancreatic cancers, and also with the lack of effective systemic therapies. Four percent of patients with adenocarcinoma of the pancreas survive 5 years after diagnosis and only 20% are alive at 1 year.[1] The median survival is 3 to 6 months. Thus, incidence rates and mortality rates are virtually identical.[1]

The early emergence of metastases in patients with exocrine pancreatic cancer suggests that chemotherapy should play a major role in the management of this disease. However, only marginal success has been achieved in identifying effective systemic therapies for pancreatic cancer and minor improvements in the survival have been noted over several decades as a result of systemic therapy (3–4% from 1975 until 2000).[2]

Most studies of single-agent or combination chemotherapy in patients with advanced adenocarcinoma of the pancreas have documented low response rates and little impact on patient's survival or quality of life. Response rates as high as 15% to 30% occasionally seen in pilot studies of novel agents or combinations have generally been difficult to reproduce in larger trials, suggesting that patient selection often accounts for apparent differences between study results.

Before approval of gemcitabine, 5-fluorouracil (5-FU) was the most extensively evaluated chemotherapeutic agent for pancreatic cancer. 5-FU alone gives response rates between 0% and 20% and the median survival does not exceed 5.5 months.[3–5] Several combinations of 5-FU with other agent were compared with 5-FU alone. The survival advantage was always nonsignificant.[6,7]

Gemcitabine is currently the only drug approved for use as single agent therapy in advanced pancreatic cancer (APC). The FDA approval in 1997 was based on the results of a randomized trial in which Gemcitabine was compared with 5-FU in previously untreated patients. Patients treated with gemcitabine had a

median survival of 5.65 months, compared with 4.41 months ($P < 0.05$) in those treated with 5-FU. Twenty-four percent of patients treated with gemcitabine were alive at 9 months, compared with 6% of patients treated with 5-FU. In addition, more clinically meaningful effects on disease-related symptoms such as pain control, performance status, and weight gain were seen with gemcitabine (23.8%) than with 5-FU (4.8%). Similar systemic effects and responses were documented in patients who were treated with gemcitabine after experiencing disease progression while receiving 5-FU.[8]

FDA approved in 2005 the use of erlotinib (Tarceva) in combination with gemcitabine for chemotherapy-naive patients with locally advanced, unresectable or metastatic pancreatic carcinoma. This approval was based on a randomized phase III trial of erlotinib plus gemcitabine (EG) versus gemcitabine. Erlotinib is an inhibitor of epidermal growth factor receptor (EGFR) activation and signaling. It is thought to exert its primary antineoplastic effects by inhibiting signal transduction pathways within cancer cells by blocking the activity of EGFR tyrosine kinase. Overall survival (OS) and progression-free survival (PFS) were statistically superior in favor of the (EG) arm.[9]

Cisplatin has also been used either with 5-FU or gemcitabine. After a trial that showed significant activity of cisplatin administered at a dose of 100 mg/m^2 every 4 weeks, cisplatin was combined with continuous-infusion 5-FU. However, poor results have been seen with both high and low-dose schedules.[10–12] The study combining fixed dose rate gemcitabine with low dose cisplatin (20 mg/m^2 dL, 8 Q21 days) has recently shown 19.1% PR and 59.6% stable disease (SD) with a median survival of 7.1 month.[13]

Oxaliplatin is a platinum compound that has a very favorable safety profile limited only by mild hematotoxicity and cumulative neurosensory toxicity reversible upon treatment discontinuation.[14] It is active in several solid tumor types, including cisplatin/carboplatin refractory disease. It has a large preclinical spectrum of anticancer activity and good activity in metastatic colorectal cancer.[15,16] In vitro studies showed a cytotoxic effect of oxaliplatin against pancreatic cancer cell lines.[17–19]

A synergistic effect has been observed with the combination of 5FU and oxaliplatin, both preclinically and in previously untreated or 5-FU-resistant metastatic colorectal cancer patients.[20,21]

One of these combinations, the FOLFOX regimens, a simplified bimonthly FA-5FU, combining high dose folinic acid (FA), and 5-FU bolus in day 1 only, and high dose infused 5-FU over 2 days, has shown to improve the response rate (RR) and prolong PFS in advanced colorectal cancer patients.[21] Recently, the FOLFOX-4 combination has become the standard treatment of adjuvant setting of colon cancer.[22] Also, this type of combination was active in gastric cancer.[23]

Recent publications showed promising results of the combination of oxaliplatin (OX) and 5-FU, continuous infusion in APC. There was no response rate for oxaliplatin alone compared with interesting results for the combined approach including 5-FU 1000 mg/m^2 perfusion day 1–day 4 and oxaliplatin 130 mg/m^2 dL every 3 weeks. The OX-FU arm showed a 10% RR compared with 0% with oxaliplatin alone.[24]

With the limited benefit from treatment with available regimens, there is a pressing need for active agents that improve survival in this poor prognosis population. Based on the above data, a study was designed to evaluate the activity and tolerance of the 5-FU/Leucovorin/oxaliplatin combination (FOLFOX-6) in patients with locally advanced (LA) and metastatic pancreatic cancer.

PATIENTS AND METHODS

Study Design and Statistical Considerations

The primary end point of this phase II study is to assess the efficacy of the combination "oxaliplatin, 5-FU and folinic acid" (FOLFOX-6) as the first-line treatment of advanced pancreatic cancer (APC), measured as an overall objective response (ORR) rate.

The hypothesis of H_0:$p_0 \leq 10\%$ versus H_a:$p_a \geq 25\%$ was tested on the basis of the ratio ORR/N, where N is the sample size.

Fleming's single-stage design[25] was applied for the sample size determination with the following rules:

- The inactivity cut-off is chosen equal to 10%, the activity cut-off equal to 25%. Hence the hypotheses of interest are H_0:r $\leq 10\%$ against H_A:r $\geq 25\%$, where r is the response rate.
- The error rate of the first type (α, probability of accepting an insufficiently active treatment, a false positive outcome) is set to 0.10.
- The error rate of the second type (β, probability of rejecting an active treatment, a false negative outcome) is set to 0.20.

The applied formula is (with normal approximation):

$$N = \left(\frac{z_{1-\beta}\sqrt{p_a(1-p_a)} + z_{1-\alpha}\sqrt{p_0(1-p_0)}}{p_a - p_0} \right)^2 \qquad (1)$$

This gives N = 25 (where z_u represents the u-quantile of the standard normal distribution).

The cp cutpoint (the number of responses to arrive at a decision) is given by the formula:

$$cp = Np_0 - 0.5 + z_{1-\alpha}\sqrt{Np_0(1-p_0)} \qquad (2)$$

This gives cp = 4 for the parameters stated above. In the derivation of this cutpoint the normal approximation was used.

The hypothesis H_a should be rejected if the number of responses ≤ 4 and the hypothesis H_0 should be rejected if the number of responses >4, with a sample size of 25.

Assuming that about 10% of the patients will be non-evaluable, 28 patients are to be enrolled in the study.

Eligibility Criteria

Eligible patients had to meet the following criteria: histologically or cytologically proven pancreatic carcinoma; nonresectable locally advanced or metastatic disease without known brain metastasis; patients without Vater's ampulloma

and adenocarcinoma of the biliary tract; no prior chemotherapy for advanced disease; adjuvant chemotherapy ended more than 12 months; at least one measurable lesion according to RECIST criteria (longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan); WHO performance status (PS) ≤2; age >18; life expectancy ≥ 3 months; no uncontrolled infection; peripheral neuropathy <grade 2 according to NCI criteria version 3.0; no other serious concomitant illness; no prior malignancy; no known allergy to one of the study drugs; adequate hematological, renal and hepatic results: neutrophil count >1500/mL; platelet count >100,000/mL, renal: serum creatinine <1.5 × the upper limit of normal value [ULN], and hepatic: SGPT <2.5 × ULN and bilirubin <1.5 × ULN functions; Pain and biliary obstruction controlled before the start of the study; absence of psychologic, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

These conditions should be assessed with the patient before registration in the trial. The protocol was approved by the Ethical Committee of the Hotel-Dieu de France University Hospital and written free informed consent was obtained from each patient.

Study Procedures

Treatment included oxaliplatin 100 mg/m^2 and folinic acid 400 mg/m^2 on day 1 followed by a 5-FU bolus 400 mg/m^2 and 46-hour infusion of 3000 mg/m^2 every 2 weeks. Patients remained on treatment until disease progression, unacceptable toxicity, patient refusal, or treatment delay >3 weeks. Calcium and magnesium perfusion, 30 mn before the oxaliplatin administration, were used systematically to all patients to prevent neurotoxicity.[26,27] Whenever possible, follow-up continued until death. In case of neutropenia >grade 2 or thrombocytopenia >grade 1, treatment was delayed for a maximum of 2 weeks and discontinued in the absence of improvement. If grade 3 or 4 gastrointestinal toxicity occurred, oxaliplatin and 5-FU doses were reduced by 20%. In the event of grade 2 or 3 hand-foot syndrome, 5-FU was reduced by 20%. Treatment was stopped for grade 4 hand-foot syndrome. In the event of continuous paresthesia/dysesthesia with pain lasting >7 days, oxaliplatin was initially reduced by 20% and subsequently by 40% if necessary. In the event of paresthesia/dysethesia with functional impairment lasting for >7 days, oxaliplatin was reduced by 40%. When paresthesia/dysesthesia with either pain or functional impairment persisted between cycles, oxaliplatin was discontinued. Medical history, clinical examination, hematology, and biochemistry laboratory tests were performed within 1 week before inclusion. Concomitant treatment was carefully checked. Tumor assessment was performed within 2 weeks before inclusion. Tumor assessment was performed using the same methods for all patients: computed tomography (CT) scan, magnetic resonance image (MRI), x-rays, ultrasounds, scintigraphy, endoscopy. Ultrasound examination was only used to detect new lesions or confirm subcutaneous skin lesions sizes. A clinical examination including a complete neurologic assessment, hematology and toxicity was performed at the end of every cycle.

Toxicity was evaluated according to The National Cancer Institute Common Toxicity Criteria Adverse Event (NCI-CTCAE version 3.0). The objective tumor response, defined according to the RECIST, was assessed every 4 cycles or earlier if clinically indicated. Objective responses had to be confirmed by imaging at least 1 month later. All radiologic examinations of patients reported as responding or with stable disease were reviewed by an independent external panel of radiologists. The time to progression (TTP) was calculated from the first treatment infusion to the first objective evidence of disease progression assessed by CT scan measurement. The overall survival (OS) was measured form initial treatment until death. The OS data was analyzed according to the Kaplan-Meier method. At the end of 4 cycles, each patient was assigned to one of the following outcomes: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), early progression, early death from malignant disease, early death from toxicity, early death because of other cause. An incorrect treatment schedule or drug administration did not result in exclusion from the RR analysis. All conclusions were based on all eligible patients. At the end of the study or earlier for those excluded for any reason, the patients were followed for at least one month, during which all procedures for the reporting of serious adverse events were followed. In the case of toxicity persisting after the end of treatment, the patient was followed until full recovery from any treatment toxicity. If feasible, post-treatment re-evaluation was pursued every 2 months until patient's death.

RESULTS

Patient Characteristics

From January 2003 through November 2004, 30 eligible patients were included in this trial. The demographic and clinical characteristics of the patients are reported in Table 1.

The median age was 65 years (range, 38–75 years) and the median WHO PS was 1 (range, 0–2). The ratio male/female was 14/16. Twenty-three out of 30 patients (73%) had metastatic disease and 27% had locally advanced cancer. The most common sites were liver (63%) and lung (17%). Of patients with metastases, 43% had one involved organ and 57% had 2 or more.

A second review of slides of those APC patients revealed one case of neuroendocrine tumor and 29 of adenocarcinoma. The patient with neuroendocrine tumor was only evaluated for toxicity. One patient had undergone prior palliative surgery for his disease. All the others had not received prior treatment.

Efficacy

A total of 181 cycles were delivered with a mean of 6 cycles/patient (extremes, 1–12). There were 23 patients evaluable for response because 2 patients had an early death, 2 patients had an early progression, 1 patient was lost of follow-up, 1 patient refused to continue the treatment, and the

TABLE 1. Pancreatic Cancer Patient's Characteristics at Baseline

Patient Characteristics	n	%
No.	30	—
Males	14	46.6
Median age (range)	65 (38–75)	—
Median performance status (range)	1 (0–2)	—
Evaluable patients	23	77
Advanced pancreatic cancer		
Locally advanced	8	27
Metastatic disease	22	73
Histology		
Adenocarcinoma	29	97
Neuroendocrine tumor	1	3
Metastatic sites		
Liver	19	63
Lung	5	17
Peritoneal carcinoma	3	10
Bone	1	3
Extra-pancreatic metastatic sites		
1	13	43
2	4	13
≥2	5	17
Prior treatment for pancreatic cancer (palliative surgery)	1	3.33

patient with neuroendocrine tumor was excluded from the evaluation. Tumor growth control marked by complete or partial response (CR or PR) or by stable disease (SD) was achieved in 62% of cases in the intent-to-treat basis (18/29 with 8 PR and 10 SD). The ORR is 27.6% [confidence interval (CI), 12–46%]. These responses were observed mainly in patients with visceral metastases (68%). Of the 8 partial response patient, 6 had metastatic disease, 3 had 3 involved organs, 1 had 2 involved organs, and 2 had one involved organ. Thus, 2 PR were noted among the 8 patients with locally advanced disease and 6 PR among the 21 with metastatic disease. Two patients had a near complete response. Detailed data are given in Table 2. The median time to progression is 4 months (range, 1–12). With a median follow-up of 27 months, median overall survival in the intent-to-treat population is 7.5 months (range, 1–20) (Fig. 1). One of the responding patients is still alive after more than 20 months. The 6-months survival and 1-year survival rates are,

TABLE 2. Efficacy Evaluation in the Intent-to-Treat Population (n = 29 eligible pancreatic cancer cases)

Characteristics	n	%
Partial response (PR)	8	27.58
Stable disease (SD)	10	34.48
Tumor growth control (PR + SD)	18	62
Progressive disease (PD)	11	38
Decrease in CA 19–9 ≥60% (n = 12 tested patients)	8	66.66

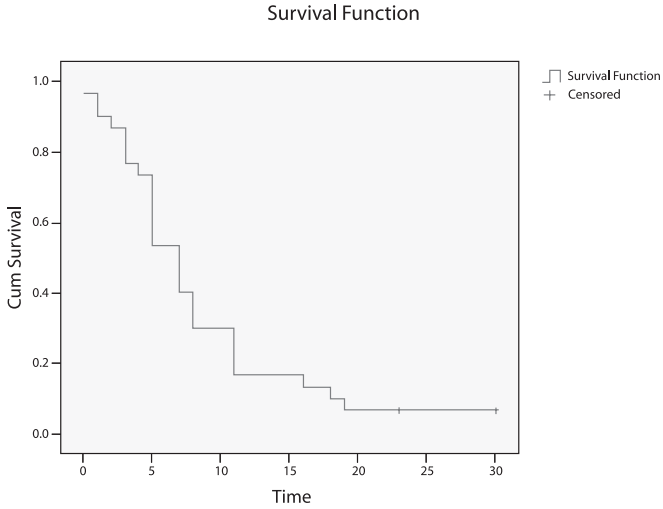

FIGURE 1. Kaplan-Meier estimates for time to overall survival intent-to-treat patients.

respectively, 55.5% (15/27 patients) and 18.5% (5/27 patients). A second-line chemotherapy (gemcitabine) was administered in 13 patients (48%). Seven patients were alive for more than 4 months and 5 patients died after 1 month after treatment.

Toxicity

All treated patients were assessed for safety according to the NCI-CTCAE version 3.0. Grade 3/4 neutropenia, assessed at the previous cycle nadir, occurred in 6 patients with febrile neutropenia in 2 patients. Grade 3/4 thrombocytopenia occurred in 3 patients, anemia in 3 patients. The most prevalent nonhematological toxicities reported were: diarrhea in 2 patients, mucositis in 1 patient, nausea/vomiting in 1 patient, asthenia in 1 patient and Gamma GT elevation in 2 patients with known hepatic metastasis. Neurosensory toxicity was mild (grade 1 in 4 patients and grade 2 in 1 patient). No toxic deaths were observed in this study. No patient had to discontinue oxaliplatin simply as a result of peripheral neuropathy. Delays of treatment of toxicity reasons was observed in 5 patients. 5-FU dose reduction was necessary in 4 and 2 patients for diarrhea and hematological toxicity, respectively. Moreover, dosages reduction of 5-FU, leucovorin, oxaliplatin were necessary in 3 patients for hematological toxicity. Toxicities are summarized in Tables 3 and 4.

TABLE 3. Hematological Toxicity

Characteristics (n = 29 patients)	Grade 1–2	Grade 3	Grade 4
Neutropenia	7	3	5 (2/5 febrile neutropenia)
Anemia	10	3	0
Thrombocytopenia	4	2	1

TABLE 4. Nonhematological Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Neuropathy	4	1	0	0
Diarrhea	0	1	2	0
Mucositis	0	4	1	0
Alopecia	4	3	0	0
Nausea/vomiting	0	3	1	0
Asthenia	1	3	1	0
Lymphangitis	0	1	0	0

DISCUSSION

Oxaliplatin is one of the new active agents in APC. Its most appropriate modality of use has not been defined yet. Cumulative neuropathy is the main side effect but is resolved upon treatment discontinuation. Given synergies with many drugs, oxaliplatin gives a higher response rate in combination. Oxaliplatin has been combined to gemcitabine in a phase II study in APC with modest results.[28] With 5-FU, preclinical data suggested synergistic efficacy which led to investigate the combination in clinical trials. In a phase II trial in pancreatic cancer patients, this combination was explored and showed encouraging response rates that deserve more evaluation.

The present study evaluated a combination of oxaliplatin (100 mg/m^2 on day 1), leucovorin 400 mg/m^2 on day 1, and 5-FU (400 mg/m^2 bolus and 3000 mg/m^2 in 46-hour infusion) every 2 weeks as first line chemotherapy for patients with advanced pancreatic cancer.

Assessment of the primary end point of the study shows an unexpected 27.6% partial response rate and 34.5% of stable disease. The response is maintained in liver metastasis. These data are encouraging in comparison with various combinations of old and new drugs in literature except targeted therapies. It showed 26.8% RR with the gemcitabine/oxaliplatin,[29] 17.3% with gemcitabine alone,[29] 12.8% with gemcitabine/CPT-11,[30] 10% with oxaliplatin and 5-FU,[24] 8.6% with the erlotinib/gemcitabine[9] and 19.1% with gemcitabine/CDDP[13] and 10.1% to 16% with the gemcitabine/capecitabine.[31–33]

Nearly one-third of the patients in this study (8 patients) had locally advanced cancer at the enrolment. These patients classically carry a better prognostic outcome that may explain, in part, the higher response rate achieved in the population analyzed. In fact, there were 2PR/8 patients with locally advanced disease and 6PR/21 patients with metastatic disease.

The 7 months median overall survival is acceptable and compares favorably to those described in the literature: 7.1 month with gemcitabine/CDDP[13]; 7.4 months with gemcitabine/capecitabine[33]; and 9 months with GEMOX in the phase III GERCOR study.[29] The 9 month median survival reported with the GERCOR phase II study (GemOx Arm) was criticized because the study was not randomized and there was a potential imbalance between the treatment groups with 5 or 6 nonmetastatic patients being found in the combination arm as well as the highest rate of patients with PS 0 to 1.[24,28]

The 12-month and the 6-month survival are 16.67% and 53.33%, respectively. The 12-month survival was 26% for gemcitabine/capecitabine and 29% for gemcitabine/CDDP.[13] The 6-month survival rate was 75% with oxaliplatin and 5-FU.[24] It is premature to reach a final conclusion in our trial regarding survival based solely on these findings.

The median time to progression was 4 months (range, 1–12) that is comparable or shorter to other reported in the literature: 4.2 months with the OXFU regimen,[24] 3.9 months with gemcitabine/cisplatin.[13] Even if patients with PS 0 to 1 (n = 19) are analyzed separately, neither median TTP nor median survival would be modified.

The toxicity profile with this combination was very acceptable, manageable and of limited significance. Unexpectedly, no grade 3 or 4 peripheral neuropathy was observed. This contrasts with results from other trials: 11% neurologic toxicity with GemOx[28] and 6% with OXFU.[24] The systematic adjunction of calcium and magnesium could partially explain our reduce neurotoxicity. Neutropenia occurred in 20% of patients at grade 3 and 4. Grade 3/4 anemia and thrombopenia were observed in 3 patients each. Two patients experienced febrile neutropenia without need of hospitalization. The nonhematological toxicities were also very mild despite the high 5-FU dose.

These data are consistent with recently reported findings from other studies with oxaliplatin combined with either 5-FU or gemcitabine.

In summary, this study provides evidence that the FOLFOX-6 regimen can be a reasonable and appropriate first line non-gemcitabine containing treatment option for patients with metastatic pancreatic cancer.

It presents a robust alternative to gemcitabine-containing regimen especially for patients who cannot be treated with gemcitabine because of its potential pulmonary toxicity, a short time interval with radiotherapy, or who have failed gemcitabine-based therapy.

This study provides interesting data and confirms that the debate FOLFOX versus GEMOX in APC is not closed. In the absence of a clear winner among the different choices, it is evident that this study merits a follow-up investigation with a phase III trial to confirm its efficacy. The concomitant or sequential incorporation of oxaliplatin/5-FU/leucovorin and gemcitabine in the treatment of APC should also be explored. We recommend in the further evaluation of this protocol to separate locally advanced disease from metastatic disease to assess the real efficacy of this regimen.

Chemotherapy and the administration of biologically active molecules, such as tyrosine kinase inhibitors, tumor necrosis factor, anti-VEGF or other targeted therapies could enhance response rates or patient survival. The study of novel chemotherapeutic agents based on the evolving understanding of the molecular biology of pancreatic cancer must continue to receive the highest priority.

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