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ORIGINAL ARTICLE

Gemcitabine plus infusional 5-fluorouracil and high dose leucovorin in advanced stage pancreatic cancer

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Summary

Purpose: *Advanced pancreatic cancer (APC) has a poor prognosis and chemotherapy remains the primary treatment modality. Gemcitabine (GEM) and 5-fluorouracil (5-FU) are the most active drugs in the treatment of pancreatic cancer. This study evaluated the efficacy and tolerability of the combination of these agents in APC.*

Methods: *Forty-four patients with APC were treated with GEM and infusional 5-FU with high dose leucovorin (LV5FU2) (GEMFUFOL regimen).*

Results: *A total of 240 chemotherapy cycles were administered. The overall response rate was 27.2%, and all responses were partial. Furthermore, disease stabilization was observed in 12 patients (27.2%). Median survival time and one-year survival rate were 9 months and 36.4%, respectively. The overall grade 3 or 4 adverse events were very low and mostly hematological.*

Conclusion: *GEMFUFOL is still an active regimen for the treatment of APC and has an acceptable toxicity.*

Key words: advanced stage, 5-fluorouracil, gemcitabine, pancreatic cancer

Introduction

Pancreatic cancer remains a fatal disease with overall 5-year survival rates less than 6% [1]. Because of its predominantly late diagnosis, most patients present with advanced-stage disease and the median life expectancy is 3-6 months [2,3]. APC is still viewed as a chemotherapy-resistant tumor. Single-agent gemcitabine is currently considered to be the standard treatment for these patients with a significant clinical benefit and survival advantage compared with 5-FU [4]. In an effort to improve therapeutic efficacy, many agents and combination schedules have been evaluated in phase II and III trials. In these trials, combination of gemcitabine with 5-FU [5], cisplatin [6], irinotecan [7] and oxaliplatin [8,9] have shown no significant increase in median survival, despite the response rate and progression free survival advantage demonstrated in the GERCOR trial [8]. Recently, results for single-agent gemcitabine have been challenged by the combination of gemcitabine and erlotinib, which demonstrated a marginal increase in median survival (6.4 vs. 5.9 months, p=0.03) in favor of the combination arm in a large randomized trial [10]. However, the improvement obtained with this combination has been only marginal, making the search for newer regimens the next logical step.

In another randomized phase III trial, capecitabine, an oral fluoropyrimidine that is currently approved and widely used for the treatment of colorectal and breast cancer [11,12], was combined with gemcitabine and this combination has been compared with gemcitabine alone in the treatment of advanced-stage pancreatic cancer. Although the combination arm failed to improve overall survival at statistically significant level compared with the standard gemcitabine arm, it has demonstrated a significant survival advantage in

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the subgroup of patients with good performance status [13]. Furthermore, in a recently published meta-analysis it has been reported a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone [2].

Capecitabine has a similar activity compared with intravenous 5-FU /leucovorin (5-FU/LV) [14] and a convenience advantage (oral administration). However, it has not been approved for the treatment of pancreatic cancer in many countries, including Turkey; also some difficulties related to the compliance concerning the regular use of oral medications can be encountered in patients with low educational level. These difficulties related to capecitabine may cause to preserve of the importance of infusional 5-FU in the treatment of pancreatic cancer.

The efficacy of 5-FU is enhanced when modulated with leucovorin and protracted infusional regimens are more effective and less toxic in colon cancer. The administration of 5-FU as protracted infusion is also active in tumors other than colorectal cancer [15]. Meanwhile, the combination of infusional regimens with newer active drugs has provided better results without decrease of doses of both drugs. In the context of colorectal cancer, regimens such as LV5FU2 were combined with irinotecan (CPT-11) and oxaliplatin, and these combinations improved the prognosis without significant increase in toxicity [16,17]. In pancreatic cancer, we adopted the same principle in order to combine two active drugs, 5-FU and gemcitabine, which have synergistic activity and non-overlapping toxicity. Previously we had published the preliminary results of this regimen in the treatment of locally advanced and metastatic pancreatic cancer [18]. Herein we present the results observed in a large number of patients with advanced-stage pancreatic cancer treated with GEMFUFOL.

Methods

Eligibility criteria

This trial included patients with pathologically confirmed adenocarcinoma of the pancreas with advanced stage. Patients with carcinomas of the biliary tract and papilla of Vater were not included. Patients with history of other cancer, prior chemotherapy or radiotherapy, uncontrolled central nervous system metastasis and uncontrolled infectious disease were excluded. World Health Organisation (WHO) performance status ≤3, age over 18 years, life expectancy over 3 months, and adequate hematological (neutrophil count >1,500/mm^3, platelet count >100,000/mm^3), renal (serum creatinine <1,5× the upper normal value-UNV) and hepatic (alkaline phosphatase <3× the UNV, bilirubin <1,5× the UNV, AST-ALT <2× the UNV) functions were the basic criteria for study inclusion. Patients were classified according to performance status (WHO performance score 0 and 1, and 2 and 3). All patients were informed about the treatment efficacy and potential toxicity.

Baseline analyses (full blood count, serum creatinine, biluribin, AST, ALT, alkaline phosphatase and CA 19.9 levels) and tumor measurement (CT scan) were performed within one month preceding the first chemotherapy cycle. Furthermore, 3 days before each cycle, physical examination, complete blood count, and serum biochemistry were performed.

Chemotherapy

The chemotherapy regimen consisted of gemcitabine 1000 mg/m^2 30-min infusion on day 1; leucovorin 200 mg/m^2 as 2-hour infusion followed by 5-FU 400 mg/m^2 bolus and 600 mg/m^2 continuous 22-hour infusion on days 1 and 2 (GEMFUFOL) (first 22 patients) and the same gemcitabine schedule plus leucovorin 400 mg/m^2 as 2-hour infusion followed by 5-FU 400 mg/m^2 bolus on day 1 and 5-FU 2400 mg/m^2 continuous 46-hour infusion (mGEMFUFOL) (next 22 patients). Treatment was repeated every 2 weeks and continued until disease progression or patient request for discontinuation. In patients with grade 3-4 hematological or gastrointestinal toxicity 25% dose reduction was done for all drugs.

Response, toxicity and survival evaluation

All of the patients had measurable or evaluable disease at the baseline evaluation, and objective tumor response was evaluated according to WHO response criteria and the best response during treatment was taken into consideration. Disease control was defined as the rate of objective response plus disease stabilization. Response evaluation was assessed by abdominal CT every 3 months, or earlier if clinically indicated. Toxicity was evaluated at each cycle according to WHO toxicity criteria. Progression free survival (PFS) was determined from the first day of treatment until evidence of clinical progression or tumor progression assessed by CT scan.

Treatment efficacy was also evaluated by serum CA 19.9 determinations which were repeated every 3 months. A decrease of 50% or more in serum CA 19.9 level was defined as serological response. A change of

<25% lower and higher from baseline value was accepted as tumor marker stabilization.

Toxicity was evaluated as each cycle according to WHO toxicity criteria.

Progression-free survival (PFS) was determined from the first day of treatment until evidence of clinical or imaging (CT scan) disease progression. Overall survival (OS) was determined from the first day of treatment until death.

Statistical analysis

Statistical analysis was performed with SPSS 15.0 for Windows. Frequency distributions of variables were performed. The chi-square test was used to compare variables and groups. Survival data were analyzed according to the Kaplan-Meier method and compared between arms using the log-rank test. All tests were two-sided and differences were considered significant when $p < 0.05$.

Table 1. Patient and disease characteristics at the beginning of treatment

Characteristics	*n (%)*
Gender	
Male	31 (70.5)
Female	13 (29.5)
Age (years)	
Median	60
Range	44-78
WHO performance status	
0	4 (9.0)
1	20 (45.5)
2	18 (41.0)
3	2 (4.5)
Site of metastatic disease (n=44)	
One metastatic site	27 (61.4)
Liver	27 (61.4)
Two or more metastatic sites	17 (38.6)
Liver+lung	10 (22.7)
Liver+lymph nodes	5 (11.4)
Liver+lymph nodes+lung	2 (4.5)

Results

From July 1998 to September 2007, 22 patients with APC were treated with GEMFUFOL and 22 with mGEMFUFOL combination chemotherapy. The baseline patient and disease characteristics are shown in Table 1. Twenty-four patients had good performance status (WHO score 0 and 1), while the remaining 20 patients had low performance status (WHO score 2 and 3). The primary tumor was located at the head of the pancreas in 28 (63.6%) patients. In 27 patients the number of involved distant organs was 1, while it was 2 or more in the remaining 17 patients (Table 1).

Response to treatment

Measurable lesions were assessable for tumor response. Objective responses were observed in 12 (27.2%) patients, and all responses were partial (95% CI: 12-40.3; Table 2). In addition, 12 (27.2%) patients showed stable disease as observed in two successive tumor assessments with a 3-month interval. Disease control rate (objective response+disease stabilization) was 54.4%. Higher tumor response was related to patients with good performance status (p=0.054; Table 2).

No significant differences between GEMFUFOL and mGEMFUFOL in terms of response rate were observed (p=0.393; Table 3). Forty out of 44 patients had adequate serum CA 19.9 measurements, permitting the evaluation of serological response. Fourteen of 40 (35.0%) patients responded. Ten of these patients had >50% decrease of CA19.9 which was accompanied

Table 2. Response and survival according to performance status

	All patients n (%)	*Good PS (WHO 0 and 1) n (%)*	*Poor PS (WHO 2 and 3) n (%)*	*p-value**
Response				0.054
Complete	–	–	–	
Partial	12/44 (27.2)	8/24 (33.3)	4/20 (20.0)	
Stable	12/44 (27.2)	9/24 (37.5)	3/20 (15.0)	
Partial + stable	24/44 (54.4)	17/24 (70.8)	7/20 (35.0)	
Progression	20/44 (45.5)	7/24 (29.2)	13/20 (65.0)	
Survival				*p-value***
Median PFS (months)	4.0	5.0	2.0	0.054
Median OS (months)	9.0	11.0	8.0	0.246

p*: Chi-square test, p**: Log rank test, PS: WHO performance status, PFS: progression-free survival, OS: overall survival

Table 3. Response and survival according to treatment regimen

	All patients n (%)	*GEMFUFOL n (%)*	*mGEMFUFOL n (%)*	*p-value**
Response				0.393
Complete	–	–	–	
Partial	12/44 (27.2)	4/22 (18.2)	8/22 (36.4)	
Stable	12/44 (27.2)	7/22 (31.8)	5/22 (22.7)	
Partial + stable	24/44 (54.4)	11/22 (50.0)	13/22 (59.1)	
Progression	20/44 (45.5)	11/22 (50.0)	9/22 (40.9)	
Survival				*p-value***
Median PFS (months)	4.0	4.0	4.0	0.643
Median OS (months)	9.0	10.0	7.0	0.969

p*: Chi-square test, p**: Log rank test, PS: WHO performance status, PFS: progression-free survival, OS: overall survival

with radiological response, while in the remaining 4 patients the disease remained stable.

Survival

With a median follow-up of 15 months, median PFS, median OS and one-year actuarial survival rates were 4.0 months, 9.0 months and 36.4%, respectively (Table 2, Figure 1 and 2). Patients with good performance status had better prognosis compared to the ones with poor performance status. In patients with good performance status, median PFS, median OS and one-year actuarial survival rates were 5.0 months, 11.0 months and 40.0% respectively, while, in patients with poor performance status median PFS, median OS and one-year actuarial survival rates were 2.0 months, 8.0 months and 31.6% respectively (p=0.054 for PFS and p=0.246 for OS) (Table 2, Figure 3 and 4). These differences were not statistically significant, obviously due to the small number of patients.

Similarly, there were no significant differences between GEMFUFOL and mGEMFUFOL in terms of survival (p=0.643 for PFS and p=0.969 for OS) (Table 3, Figure 5 and 6).

Toxicity

Two hundred and forty chemotherapy cycles were administered (median 9, range 2-30). Median duration of treatment was 17 weeks. No treatment interruption

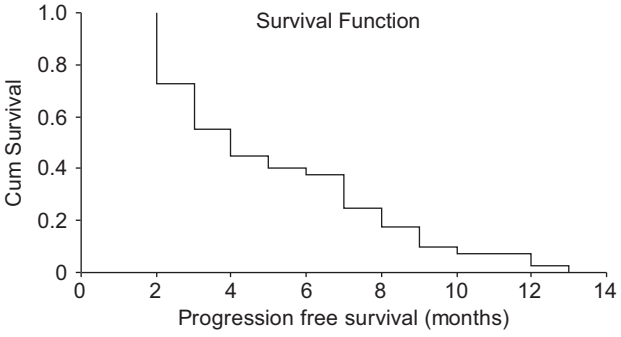

Figure 1. Progression-free survival of all patients.

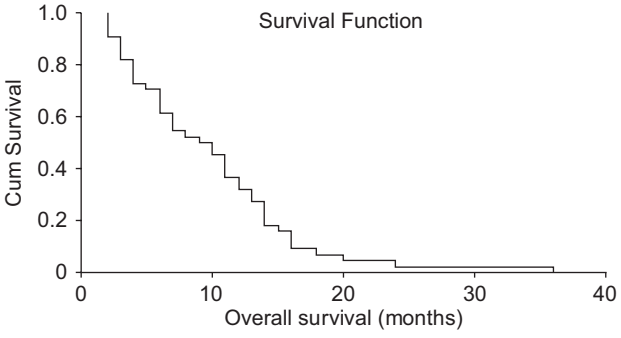

Figure 2. Overall survival of all patients.

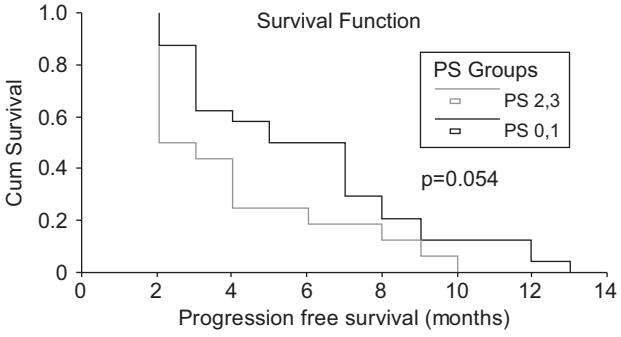

Figure 3. Progression-free survival according to performance status.

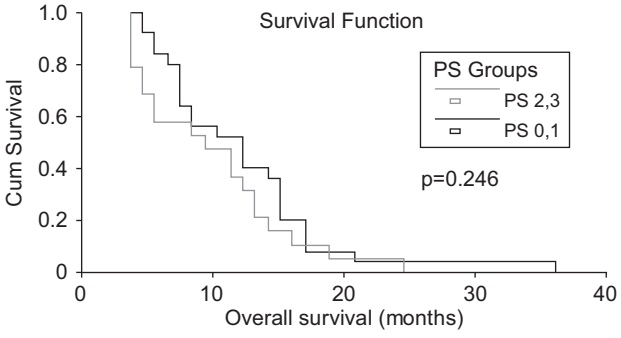

Figure 4. Overall survival according to performance status.

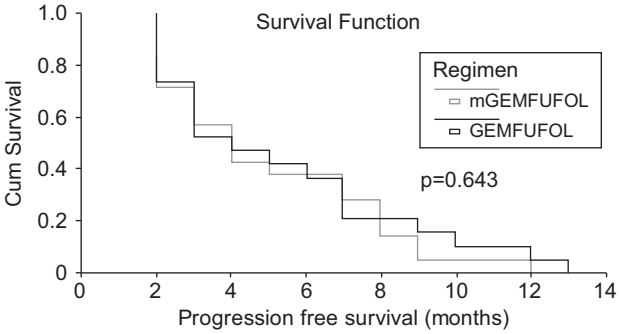

Figure 5. Progression-free survival according to treatment regimen.

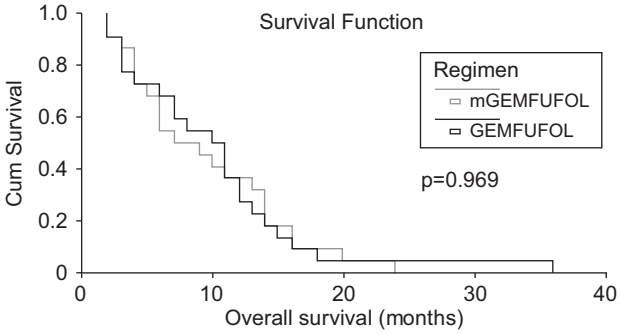

Figure 6. Overall survival according to treatment regimen.

Table 4. Grade 3-4 toxicities

Toxicity	*n (%)*	*GEMFUFOL n (%)*	*mGEMFUFOL n (%)*
Neutropenia	2 (4.5)	0 (0.0)	2 (4.5)
Thrombocytopenia	2 (4.5)	1 (2.2)	1 (2.2)
Nausea and vomiting	4 (9.1)	2 (4.5)	2 (4.5)
Mucositis	4 (9.1)	1 (3.1)	3 (6.0)
Diarrhea	2 (4.5)	0 (0.0)	2 (4.5)
Alopecia	6 (13.6)	3 (6.8)	3 (6.8)

occurred in any patient, while 25% dose reduction of all drugs was necessary in 4.5% of the patients due to grade 3-4 hematological and gastrointestinal toxicity and treatment delays were necessary in 9% of the patients due to inadequate hematological parameters (neutropenia and thrombocytopenia). The dose intensity related to the planned doses was 94% for gemcitabine and 94% for 5-FU. Severe toxicities were exceptional. Alopecia, mucositis and nausea-vomiting were the most common toxicities (13.6, 9.1 and 9.1%, respectively). Only 2 patients had severe hematological toxicity; in 2 cases neutropenia was not accompanied with fever and in another 2 cases thrombocytopenia improved without platelet transfusion (Table 4). There was no treatment-related death. No patient required red blood cell transfusion. We did not find any difference in terms of toxicity between patients treated with GEMFUFOL and mGEMFUFOL.

Discussion

Forty-four patients with advanced-stage pancreatic cancer were treated with a bimonthly regimen consisting of 5-FU, high-dose leucovorin and gemcitabine. Objective response rate 27.2%, median survival 9.0 months and one-year actuarial survival rate 36.4% were obtained. This regimen was well tolerated and toxicity was very low. Twenty-two patients received 5-FU in 2 consecutive days (total 5-FU dose 2000 mg/m^2 in each cycle), while the next 22 patients were treated with 46-hour infusion of 5-FU (total dose 2800 mg/m^2 in each cycle). This schedule was adopted from the changes in the treatment of colorectal cancer in which the 5-FU infusion repeated on two consecutive days was replaced by a unique 46-hour infusion few years ago. However, no difference in terms of efficacy and toxicity between GEMFUFOL and mGEMFUFOL was registered.

Metastatic pancreatic cancer is an incurable disease and systemic chemotherapy, which is the main treatment modality in this setting, can result only in limited response rates, not exceeding 20% [19]. Because chemotherapy is only marginal in this disease, the aim of treatment is palliative, and attention should be paid to toxicity when selecting a chemotherapeutic regimen [20].

In the literature there is a heterogeneity about the chemotherapeutic regimens used in the treatment of advanced-stage pancreatic cancer, however, two metaanalyses that included a large number of patients have demonstrated that there was a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone [2,21]. Based on phase III trials and metaanalyses, gemcitabine is a widely accepted and moderately active standard treatment for APC. However, several other active drugs have been evaluated in phase II trials to be combined with gemcitabine in patients with APC [7,22]. In this context, 5-FU has been an attractive and mostly used agent with the advantages of favorable toxicity profile and synergistic effects. Although the dose and schedule of administration of gemcitabine has been similar in nearly all the trials, the administration of 5-FU varied from protracted continuous infusion to bolus infusion with various intervals and doses [21-36]. In these trials protracted infusions have shown slightly better results than bolus administrations with respect to efficacy and toxicity despite disadvantages of the schedule administration.

The LV5FU2 regimen has a better activity in advanced colorectal cancer when compared with the Mayo regimen and toxicity is much lower [15]. There is a lot

of data indicating that this regimen can be combined with other drugs without need for dose reduction. Good examples were the combination with CPT-11 [16] and oxaliplatin [34] in the treatment of colorectal cancer. In these trials which led to new standards in the treatment of advanced colorectal cancer, 5-FU was combined with CPT-11 and oxaliplatin without dose reduction and the efficacy was higher without significant increase in toxicity. In the absence of cross resistance or incompatibility between gemcitabine and 5-FU, these two drugs were combined to treat pancreatic cancer. The gemcitabine dose and administration schedule was adjusted to LV5FU2 regimen.

In a recently published randomized phase III trial, the efficacy and toxicity of capecitabine pus gemcitabine was compared with single-agent gemcitabine. The combination arm ha shown similar OS and toxicity profiles compared with the single-agent gemcitabine arm. However, in *post hoc* analysis, a significant survival advantage was found in the subgroup of patients with good performance status in favor of the combination arm [13].

In our trial, similar results to the above mentioned trial were obtained. This may be due to the similarity of gemcitabine dosage and patient characteristics in both trials. Good performance status has been reported as an important factor positively impacting the combination arm in another study that compared cisplatin plus gemcitabine combination with gemcitabine alone [6]. This may be explained party by the hypothesis that patients with a good performance status may have a greater benefit for treatment intensification. This fact has also been supported by a recent pooled analysis [35]. However, in our study we failed to show any significant difference when we compared the efficacy of mGEMFUFOL (in which higher 5-FU dosage was administered) to GEMFUFOL.

Capecitabine has a similar activity and toxicity profile compared with intravenous 5-FU /leucovorin (5-FU/LV) [14], but has the convenience of oral administration. However, compliance to oral treatment can be encountered in many patients, especially in those with low educational level. Furthermore, the alterations in the motility, digestion and absorption can affect the biologic availability of the drug and lead to variable plasma drug levels. This may also be very important in patients with pancreatic cancer. Pancreas is a main source of the digestive enzymes acting in the small intestine and its disorders can be accompanied by alterations in the absorption of nutrients and drugs. These difficulties related to capecitabine as an oral drug may make the infusional 5-FU an alternative choice in the treatment of pancreatic cancer. So, we use a regimen combining infusional 5-FU with gemcitabine in the treatment of pancreatic cancer.

It is generally accepted that response evaluation by imaging methods is difficult in pancreatic cancer, mainly due to desmoplastic and inflammatory reactions of the tumor [6]. Furthermore, discrepancy in the assessment of tumor response by WHO and RECIST criteria in patients with pancreatic cancer was reported, showing that clinical presentations were more consistent with WHO categorization [36]. For this reason the disease control rate may give more reliable results about the drug efficacy rather than response rate evaluation. Disease control rate is 42-44% with single-agent gemcitabine [37,38], while the combinations of gemcitabine with cisplatin and 5-FU consistently increased it to 55-68% [38-41] and 40.4-46% respectively [42,43]. In our trial disease control rate was 54.4%.

Current research strategies on pancreatic cancer are increasingly evaluating combination regimens to overcome chemotherapy resistance as well as building up effective chemotherapy platforms with the addition of the so-called targeted agents to exploit multiple potential oncogenic pathways.

In conclusion, the present study is one of the few trials of gemcitabine and infusional 5-FU/LV combination. As expected, toxicity was very low and the efficacy was at least not less compared to standard regimens used in the treatment of cancer of the pancreas. With the addition of novel agents, GEMFUFOL may show more efficacy in the treatment of advanced-stage pancreatic cancer.

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