ORIGINAL ARTICLE

Comparison of Clinical Effectiveness of Folfirinox versus Gemcitabine on Quality of Life in Patients with Pancreatic Cancer Stage IV

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Abstract

Objective: The aim of this study is to assess the clinical effectiveness of folfirinox (Fol) compared with gemcitabine (Gem) on quality of life (QOL) that predicts survival in patients with Stage IV of pancreatic cancer. **Materials and Methods:** A total of 34 patients suffering from metastatic pancreatic adenocarcinoma were randomized into two groups, the Gem group (n = 17) and Fol group (n = 17). The first group was treated with Gem in a dose of 1000 mg/m^2 once weekly for 7 weeks, followed by 1 week of rest during the first cycle and subsequently 1000 mg/m^2 once weekly for 3 weeks followed by 1 week of rest. The second group was treated with Fol (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus, followed by 2400 mg/m^2 on 46-h continuous infusion) once every 2 weeks. The QOL was measured by the functional assessment of cancer therapy (FACT)-hepatobiliary cancer scale. **Results:** Thirty-four of randomized patients completed the study, and there were no significant differences among the two groups at baseline demographic characteristics. Overall QOL, P value shows the significance of correlation for components of FACT in all scales between Fol-group and Gem-group. Median survival time for the entire cohort was 14.1 months for Fol-group compared to Gem-group which was 9.2 months. P value shows the significance of the correlation between survival rate and stage of tumor, in Fol-group versus Gem-group (P = 0.0001). **Conclusions:** We conclude that Fol significantly improves QOL, physical functioning and survival time in advanced pancreatic cancer patients in comparison with Gem.

Key words: Clinical effectiveness, folfirinox, gemcitabine, pancreatic cancer, quality of life

INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer death in Europe and USA[1,2] and the seventh most common cause of cancer death in Kosovo. Three-quarters of deaths are in people over 60 years old.[3]

It is an aggressive disease which usually causes no symptoms in its early stages, making it difficult to diagnose.[4,5] Initial symptoms may include severe pain in the back or stomach area, unexpected weight loss, jaundice, feeling sick, diarrhea, weight loss, and loss of appetite, which can severely reduce a patient's quality of life (QOL).[6] The definition of pancreatic cancer Stage IV means cancer has spread to other organs in the body, such as the liver, lungs, stomach, spleen, and/or the bowel.[7] The symptoms may appear only toward the later stages of the illness, so the majority of patients present with advanced stage disease. As such, there are rarely more than a few months between diagnosis and death.[8]

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In this context of limited survival, QOL assumes great importance and its improvement must be the main treatment goal.[9]

People with locally advanced or metastatic disease may be offered chemotherapy, radiotherapy or palliative surgery to help control tumor growth and symptoms.[6] For the majority of the suffering patients palliative care is the best treatment that can be offered.[8]

Gemcitabine (Gem) is a chemotherapy treatment that is toxic to cancer cells by stopping a part of the cancer cell replicating itself.[10] It has been considered the standard treatment for locally advanced or metastatic adenocarcinoma of the pancreas because has a wider spectrum of antitumor activity due to its different cellular pharmacology and mechanism of action.[11,12] The cytotoxic effects of Gem are exerted through incorporation into DNA resulting in inhibition of DNA synthesis and replication at several steps.[13,14]

Folfirinox (Fol), is a combination of oxaliplatin, irinotecan, leucovorin, and fluorouracil, emerged as an effective non-Gem containing regimen for metastatic pancreatic cancer.[15]

The aim of this randomized study is to assess the clinical effectiveness of Gem versus Fol on QOL in patients with Stage IV of metastatic pancreatic cancer.

MATERIALS AND METHODS

Patients and treatment

A systematic search for QOL and clinical effectiveness of Gem versus Fol in pancreatic cancer patients were performed.

The trial was conducted at the Clinic of Oncology of the University Clinical Center of Kosovo. All participants received and signed a copy of the informed consent form following the procedures approved by the Ethical Board of the Faculty of Medicine, University of Kosovo.

A total of 50 pancreatic cancer patients from Oncologic Institute of Kosovo were recruited to the trial from January 01 to December 31, 2015.

Eligibility criteria for participating in this study were histologically confirmed Stage IV pancreatic cancer. Patients at Stage I-II and III of pancreatic cancer were not admitted to the trial.

Patients who had fulfilled the eligibility criteria were 34. Randomization of patients into the groups was made based on their performance status. Patients who had a good performance status (Eastern Cooperative Oncology Group 0 or 1), no unstable angina or cardiac ischemia, normal or nearly normal bilirubin levels <1.5 UNL, normal hepatic, hematopoietic and renal function, age 18-75, were randomized in Fol group (n = 17). Other patients with poor performance status were randomized in the Gem group (n = 17). The similar number of patients in both groups was just a coincidence.

In the first group, patients were treated with Gem in a dose of 1000 mg/m^2 once weekly for 7 weeks, followed by 1 week of rest during the first cycle and subsequently 1000 mg/m^2 once weekly for 3 weeks followed by 1 week of rest.

In the second group, patients were treated with Fol (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 400 mg/m^2 bolus, followed by 2400 mg/m^2 on 46-h continuous infusion), once every 2 weeks.

University Hospital and Clinical Service of Kosovo by Decision No. 05/148 supplies clinics with medicines and medical equipment.[16]

On the initial visit, a written informed consent was obtained from participants, who then responded to a demographic and health status questionnaire. Patients in both groups were followed for 12 weeks. For 12 consecutive weeks, patients of Gem group received 10 cycles of chemotherapy, while patients of Fol group received 6 cycles of chemotherapy. At the end of 12 weeks, patients were re-evaluated by health-related QOL questionnaire.

Outcome measures

Demographic data (name, age, education level, and employed/unemployed) were collected by self-report. Medical data (the number of days since the diagnosis, cancer stage, performance status, medication, type of treatment, surgery, and radiotherapy) were collected from medical records.

QOL assessment

The primary outcome measure was the impact of Gem versus Fol on QOL, as measured by the Functional Assessment of Cancer Therapy-Hepatobiliary cancer (liver, bile duct and pancreas) (FACT-Hep) scale.[17]

The FACT-Hep questionnaire is safe, and an effective tool for measuring health-related QOL for patients with pancreatic cancer. This self-report questionnaire is appropriate for administration to patients at various stages in the disease process and has shown demonstrable reliability and validity in assessing patients physical and functional status.[18]

The FACT-Hep contains specific subscales assessing physical well-being (seven questions), social/family well-being (seven questions), emotional well-being (six questions), functional well-being (seven questions), and additional concerns (18 questions). Patients answered to questions on a five-point scale ranging 0 (not at all) to 4 (very much).

For physical, emotional, and additional scales, a high score indicates more symptoms and more difficulties. For social/family and functional scales, a high score indicates better function and better QOL.

Data analysis

Analysis of findings from the FACT questionnaires followed FACT guidelines.[15] The collected data were analyzed with SPSS Version 22 program. Qualitative data were analyzed with χ^2-test and Fisher test, while quantitative data were analyzed with *t*-test and Mann–Whitney. Kaplan–Meier survival analysis was used to show the survival rate between two groups. A $P < 0.05$ shows the criterion for statistically significant results. The focus of the analysis was to test whether significant differences existed between the age of patients, components of FACT, surgery, radiotherapy, stage of cancer, QOL, and clinical effect of the treatment.

RESULTS

Table 1 summarizes demographic and medical characteristics of the 34 patients who participated in this study. From 34 patients at Stage IV, 17 (50%) were treated with Gem (arm) and 17 (50%) were treated with Fol (arm). Baseline demographic and clinical characteristics were approximately similar for both treatment arms. Median age for Gem arm is 68 years (range 59-79 years), 13 males (76%), 4 females (24%), 5 (29%) of the patients had completed a college education, and 2 (12%) were employed full-time. While for Fol arm is 65 years (range 56-77 years), 10 males (59%), 7 females (41%), 5 (29%) of the patients had completed a college education, and 2 (12%) were employed full-time. In Gem arm, none of the patients underwent surgery, as far as in Fol arm 8 patients (47%) underwent surgery, where 3 (18%) of them had whipple's pancreaticoduodenectomy ($P = 0.227$), while 5 (29%) had gastroenterostomy ($P = 0.045$). In both arms, none of them patients went through radiation therapy.

Table 2 is listed the outcomes of QOL measures. 34 randomized patients (100%) completed a baseline FACT-Hep questionnaire before treatment, and the baseline values were not significant between two groups. After 12 weeks of treatment, *P* value shows the significance of correlation for components of FACT in all scales between Fol arm and Gem arm. Physical well-being ($P = 0.016$), social/family well-being ($P = 0.027$), emotional well-being ($P = 0.028$), functional well-being ($P = 0.0001$), and additional well-being ($P = 0.0108$). All of these scales shows significant *P* value between two groups after 12 weeks of treatment in favor of Fol arm.

Table 1: Baseline demographic and clinical characteristics

Characteristics	Grupet		*P* value
	Gem *n*=17	Fol *n*=17	
Age (year)			
Mean±SD	68.6±5.9	65.8±7.7	0.249
Rank	59-79	56-77	
Gender *n* (%)			
Male	13 (76.5)	10 (58.8)	0.463
Female	4 (23.5)	7 (41.2)	
Stage of education *n* (%)			
High	5 (29.4)	5 (29.4)	0.641
Medium	10 (58.8)	8 (47.1)	
Low	2 (11.8)	4 (23.5)	
Employed full-time (>39 h/week)			
No	15 (88.2)	15 (88.2)	1.00
Yes	2 (11.8)	2 (11.8)	
Tumor stage			
IV	17 (100.0)	17 (100.0)	
Whipple's pancreaticoduodenectomy			
No	17 (100.0)	14 (82.4)	0.227
Yes	-	3 (17.6)	
Gastroenterostomy			
No	17 (100.0)	12 (70.6)	0.045
Yes	-	5 (29.4)	

SD: Standard deviation, Gem: Gemcitabine, Fol: Folfirinox

Table 2: The effect of Gem/Fol on QOL outcomes

Group	Baseline		Post-intervention	Change	Difference between groups		*P* value
	Mean±SD	*P* value	Mean±SD	Mean±SD	Mean change	95% CI	
Physical well-being (0-28) 7q							
Gem	10.4±1.9	0.104	17.8±1.7	7.5±2.1	8.3	8.1-8.4	0.016
Fol	11.3±1.3		20.4±1.5	9.1±1.5			
Social/family well-being (0-28) 7q							
Gem	10.7±1.6	0.193	22.9±1.7	12.2±2.6	13.4	13.3-13.6	0.027
Fol	10.0±0.9		24.6±1.6	14.6±1.5			
Emotional well-being (0-24) 6q							
Gem	11.2±1.7	0.225	15.4±0.6	4.2±1.8	5.2	5.1-5.3	0.028
Fol	11.9±1.0		18.2±1.5	6.2±1.9			
Functional well-being (0-28) 7q							
Gem	6.7±0.8	0.09	10.2±2.0	3.5±2.5	5.5	5.3-5.7	0.0001
Fol	6.2±1.0		13.6±1.5	7.5±1.7			
Additional concerns (0-72) 18q							
Gem	21.4±1.5	0.188	38.6±2.4	17.3±2.4	18.5	18.3-18.6	0.0108
Fol	21.9±0.9		41.5±2.4	19.6±2.7			

CI: Confidence interval, QOL: Quality of life, SD: Standard deviation, Gem: Gemcitabine, Fol: Folfirinox

Table 3 summarizes the survival rate of patients. On average, in Gem arm 17.6% (3 patients) lived 3-5 months, 29.4% (5 patients) 6-8 months, 23.5% (4 patients) had a median of survival from 9 to 11 months, and about 29.4% of patients (5 patients) survived beyond 12 months. While in Fol arm about 5.9% (1 patient) lived 6-8 months, 11.8% (2 patients) had a median of survival from 9-11 months, and about 84.2% of patients (14 patients) survived beyond 12 months.

Median survival time for the entire cohort was 9.2 months (range 1-24 months) for Gem arm, whereas for Fol arm median survival time was 14.1 months. *P* value shows a significance of correlation of survival rate between two groups of patients, Fol arm compared to Gem arm, respectively ($P = 0.0001$) [Table 3].

Kaplan–Meier survival curve also shows that survival time is higher in Fol group in comparison with Gem group [Chart 1].

Table 3: The survival rate of patients by groups

Survival rate (months)	Group		Total
	Gem	Fol	
	N (%)	*N* (%)	*N* (%)
3-5	3 (17.6)	0 (0.0)	3 (8.8)
6-8	5 (29.4)	1 (5.9)	6 (17.6)
9-11	4 (23.5)	2 (11.8)	6 (17.6)
12-18	5 (29.4)	14 (82.4)	19 (55.9)
Total	17 (100.0)	17 (100.0)	34 (100.0)
Mean±SD	9.2±3.3	14.1±3.2	11.6±4.1
P value	<0.0001		

SD: Standard deviation, Gem: Gemcitabine, Fol: Folfirinox

DISCUSSION

We prospectively investigated QOL in patients receiving Fol versus Gem and survival time among these points. There was no indication of a treatment difference, with the exception of a minor improvement in QOL and survival possibility in favor of Fol.

Gem, for the last couple of decades in a lot of clinical trials[19-23] has been considered the reference standard treatment in advanced pancreatic cancer as a first line treatment or a Gem based combination regimen in improving QoL of patients, but all of them have provided disappointing results in the way of survival possibility.

Our findings were significantly associated with survival, after controlling for the effects of Stage IV at diagnosis. The overall median survival time was 14.1 months in the Fol group with a survival advantage, as compared with 9.2 months in the Gem group ($P < 0.0003$). These

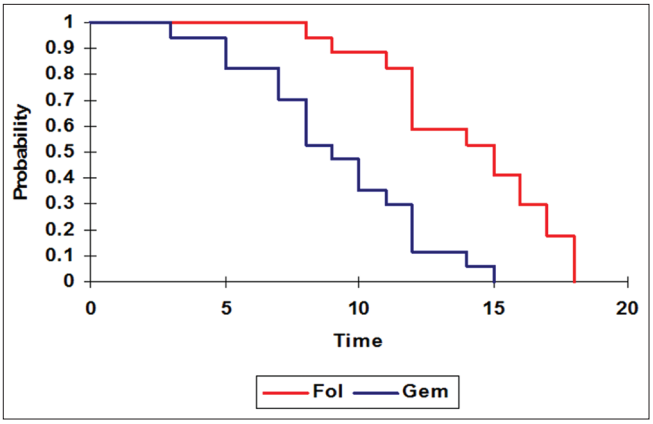

Chart 1: Kaplan–Meier survival curve

findings of our study are in accordance with several other studies.[15,24,25]

Conroy T, *et al*. concluded that median survival was 11.1 months in the Fol group as compared with 6.8 months in the Gem group ($P < 0.001$).[23] Singhal *et al*. concluded that median overall survival was 10.8 months in the Fol group as compared with 7.4 months in the Gem group ($P < 0.001$).[26]

The findings in this study show that the clinical effect of Fol compared with Gem may improve the QOL of patients with pancreatic cancer. This is also in accordance with other studies,[15,25-29] which show beneficial effects of Fol versus Gem in overall QOL and psychological distress.

Physical and social well-being were good in both arms. Almost all the patients reported positive aspects in terms of life improvement and coping with the disease. However, patients in Fol group claimed feeling physically stronger, able to walk and even do light physical exercises after receiving the chemotherapy than Gem group. While, general pain, fatigue, weight loss, and dissatisfaction with their appearance were more prevalent in patients of Gem group, due to its severe toxicity profile. These results are also supported by other studies on similar program of therapy,[15,25-28] for the efficacy Fol therapy in improving the overall QOL and psychological distress.

Patients in Fol group did complained of diarrhea and vomiting more than Gem group because the use of Gem therapy has been shown to be well tolerated. Our results confirmed previous published evidence.[15,29,30]

The emotional well-being part shows some specific aspects of QOL, including the psychological burden associated with insecurity. In Gem arm, patients had the feeling of fear that their situation will worsen continually or the worry they relatives might be hit by the disease too. Among these aspects, there is also a continuing hope for cure and survival. Other authors also concluded that Gem did not improve QOL for patients who respond to treatment, so it did affect their emotional and functional status.[31,32]

The functional well-being is also better in fol arm compared to Gem arm. Patients in fol arm claimed that it helped them to cope better with depression and anxiety. Also in accordance with other studies.[15,25-29,31,32]

Otherwise, of our findings, there are other studies[24,30] who have concluded that Fol significantly reduces QOL impairment in patients with metastatic pancreatic cancer, because of the increased toxicity of Fol.

Even though there are differences in the above studies,[19-32] most of them conclude that Fol compared to Gem improves the overall QOL.

The limitations of our study are the small number of patients, and the results based on such a small number may not be considered as definitive. The diagnosis of pancreatic cancer is still dismal and has a profound impact on QOL, which is an important issue, whereas in future studies a huge attention must be paid to a patient's pain control and functional symptoms, psychosocial needs and nutritional status.

Whereas further improvement is obviously needed, these results are stimulating and encouraging. In pancreatic cancer this is a relatively small victory, because part from all the advanced research studies in oncology, the prognosis of pancreatic cancer unfortunately still remains very poor and for those patients with a short remaining time of life, especially for those who are younger, this time is considered extremely valuable, and for this reason relief of symptoms and survival must be balanced with social and functional injury, to define better approaches regarding patient's personal needs. Therefore, well-designed prospective studies with better strategies and new agents in the treatment of advanced pancreatic cancer are needed in the future.

CONCLUSIONS

This study demonstrates that chemotherapy with Fol compared to Gem seems to significantly improve QOL and survival time in these patients. The impact of therapy with Fol on tumor-related symptoms (pain, performance status, and weight) was believed to have relevant positive change, so a patient may have clinical benefit and improved QOL. Furthermore, there is evidence of a small survival possibility. The QOL satisfaction of patients with pancreatic cancer measured by the FACT-Hep provides helpful information and they may have significant implications, as well as relief in getting clinical decisions.

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