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Original article

Palliation with Previously Gemcitabine in Patients with Advanced Pancreatic Cancer Treated with the Placement of a Covered Metal Biliary Stent

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SUMMARY

Background/Aim: To evaluate the efficacy of gemcitabine as palliation in patients with advanced pancreatic cancer (PC) previously treated with the placement of a covered metal biliary stent, taking into account survival and quality of life (QoL). Methods: Forty-nine patients with unresectable PC, and obstructive jaundice previously treated with the placement of a covered metal endoprosthesis, were randomized to receive gemcitabine (Group A: 9M,7F) or to followed without any anticancer intervention (Group B: 18M,15F). Gemcitabine was administered weekly as an intravenous 30 min infusion of 1000 mg/m² for 3 consecutive weeks followed by a 1-week rest in each cycle (28 days). QoL was evaluated with the QLQ-C30 questionnaire. Results: 229 gemcitabine doses were administered [median 14.3 doses per patient (range 7-22)]. No statistically significant differences were observed regarding the survival (Group A: median 21 weeks, range 13-33, Group B: median 22 weeks, range 13-29, p=0.809). According to the average QLQ-C30 score for each patient, Group B presented statistically significant higher values (p=0.0001). Leucocytopenia, neutropenia, thrombocytopenia and anemia were the most common side effects in group A (81.25%, 68.75%, 56.25%, 31.25% respectively). Conclusion: Gemcitabine didn't show to improve survival and QoL in patients with advanced PC previously treated with a covered metallic endoprosthesis due to obstructive jaundice.

Key Words: gemcitabine, jaundice, metal covered biliary stents, pancreatic cancer, quality of life, survival

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Pancreatic cancer (PC) is a common, highly lethal disease world-wide. Approximately 40,000 new cases occur every year in Europe and almost 30,000 in the United States.[1,2] It is one of the few cancers the mortality rate of which nearly equals its incidence.

Although complete surgical resection is the only potentially curative treatment approach, only 20% of patients present with truly resectable disease. The vast majority have unresectable or metastatic disease at the time of diagnosis, many of whom will die within 4 to 6 months.

Because of this dismal natural history, palliation remains the cornerstone of management for patients with PC and must be directed towards relief of intractable pain, gastric outlet obstruction and biliary obstruction.[3] Obstructive jaundice occurs in 70-90% of patients with PC and may result in numerous complications such as malabsorption and consequent progressive malnutrition, cholangitis, pruritus and progressive hepatocellular dysfunction.[4,5]

Palliative relief of biliary destruction due to PC may be accomplished with surgical, radiological or endoscopic techniques. Although the effectiveness of these methods is similar, surgical and radiological procedures are associated with substantial morbidity and mortality.[6] Thus, palliative biliary stenting via the endoscopic transpapillary route has become the treatment of choice for these patients, decreasing the incidence of complications from malignant obstructive jaundice and improving the quality of life (QoL).[7]

On the other hand, radiation therapy, chemoradiation and combination chemotherapy have not shown to improve the overall survival rates of patients with unresectable disease. Only two chemotherapeutic agents, 5-fluorouracil (5-FU) and gemcitabine, have been associated with a reproducible survival of more than 5 months. Compared to 5-FU in terms of quality of life and survival, gemcitabine, is accepted today as the standard first-line agent for the treatment of patients with advanced PC.[8]

The aim of this prospective randomized controlled trial was to evaluate the efficacy of gemcitabine administration in terms of survival and QoL in patients with unresectable carcinoma of the pancreatic head, previously treated with the placement of an autoexpandable covered metallic biliary endoprostheses due to obstructive jaundice.

PATIENTS AND METHOD

Eligibility criteria for the entry in the study were: written informed consent, 25-75 years of age, diagnosis of PC confirmed either by cytological or histological evidence of tumor tissue, locally advanced disease with no history of prior anticancer therapy and no indication of radiotherapy, absence of duodenal obstruction, no previous biliary stent placement and no history of previous gastrectomy, choledochoduodenostomy, choledochojejunostomy or hepaticojejunostomy, estimated life expectancy more than 3 months, Karnofsky performance status more than 50%, adequate pulmonary ($PaPO_2 \geq 70$ mmHg) and renal (normal blood urea and serum creatinine levels) function, satisfactory liver biochemistry after stenting (total bilirubine level ≤2 times than the upper normal limit, ALT and AST levels ≤2 times than the upper normal limit), INR≤1.4, adequate bone marrow reserve (WBC within the normal limits, neutrophil count ≥2000/mm³, PLT≥100.00/mm³, Hb≥10 g/dl) and no evidence of viral, autoimmune and hereditary liver disease.

The exclusion criteria were: concomitant malignancy, central nervous system metastatic disease, severe heart disease, severe neurological impairment or mental disorder, diabetes mellitus difficult to control, pulmonary fibrosis or interstitial pneumonia, marked peripheral edema, marked pericardial or pleural effusion, active infection, pregnancy and lactation, uneffective contraception for females of childbearing age and severe drug hypersensitivity.

A total of 73 patients with obstructive jaundice due to advanced PC, previously treated endoscopically with the placement of an expandable metal biliary stent (Wall stent Endoprosthesis-Boston Scientific), were assessed for eligibility.

Twenty four of the above patients were excluded from the study (16 failed to satisfy inclusion criteria, 6 refused to participate, 2 for other reasons).

Finally, 49 patients were allocated into the two treatment arms. For each patient on gemcitabine two control patients were selected. Sixteen of whom-Group A (9 men and 7 women) received gemcitabine and 33-Group B (18 men and 15 women) were followed up without any further treatment. Gemcitabine treatment was started 3-5 days after endoprosthesis placement (mean time 4 days). The only intervention allowed for both groups was the placement of a plastic biliary endoprosthesis when occlusion of the metal stent required. Patients` allocation into the two arms was based on a sequence of random binary numbers (i.e. 111100111010…) that was developed in a computer based program. No statistically significant differences regarding sex (p=1,000) and the age (p=0,948) of the participants were observed among the study groups (Table 1).

The duration of follow-up was decided at 12 months.

The study protocol was approved by the hospital ethics committee.

Pre-stenting evaluation included all the laboratory tests reported in the eligibility criteria plus an electrocardiogram, chest radiography, upper abdominal ultrasonography and upper abdominal CT scans.

During endoprosthesis placement and the first course of gemcitabine treatment, patients were hospitalized. Further treatment with gemcitabine was administered on an outpatient basis when their general condition remained satisfactory and no serious adverse events had occurred.

Gemcitabine was administered as an intravenous 30 min infusion of 1000 mg/m² per week for 3 consecutive weeks followed by a 1-week rest in each cycle of 28 days.

Development of serious adverse effects and/or complications (hematological toxicity, renal failure, jaundice ≥4

Table 1. Baseline characteristics of the two studied groups

	Group A	Group B	p value
Number	16	33	
Sex (male)	9	18	1.000
Age	57-72	55-69	0.948
Metastatic Disease	6	12	0.912
Bilirubine	1.85	1.79	0.789
ALT	72	67	0.844
AST	59	61	0.933
Hemoglobin	11.8	12.1	0.767

times than the upper normal limit, grade 3 nausea/vomiting) and a request to withdraw were reasons for removal from the study.

There was no routine prophylactic administration of antihemetics or granulocyte colony-stimulating factors.

As primary end point of the study, the evaluation of survival in weeks, between the two groups was determined. The evaluation of QoL for the patients of both groups, measured monthly with the use of the QLQ-C30 EORT questionnaire, was determined as the secondary end point. The QLQ-C30 includes a total of 30 questions or "items" and is composed of scales that evaluate physical (five items), role (two items), emotional (four items), cognitive (two items) and social (two items) functioning, as well as a global health/QoL scale. Higher scores on these scales represent better functioning. There is also three symptom scales measuring nausea and vomiting (two items), fatigue (three items) and pain (two items), and six single items assessing additional symptoms (dyspnoea, sleep disturbance, constipation, diarrhea, and loss of appetite). The placement of a second plastic biliary stent and the hematological toxicity of gemcitabine (leucopenia, neutropenia) were also evaluated.

STATISTICAL ANALYSIS

The Students t-test was employed to investigate QLQ-C30 score differences between the two examined groups of patients in each visit.

Survival distribution curves were compared by log-rank statistic.

RESULTS

The patients from group A received a total of 229 doses of gemcitabine, each one with a mean value of 14.3 doses (range 7-22). Request to withdraw was the reason for treatment discontinuation in one case. In the remaining 15 patients gemcitabine was not administered in the last 2-3 weeks before death when their state of health was very serious.

Survival: At the end of the follow up period we had only «fatal events». No statistically significant difference was observed between the two studied groups regarding the survival of our patients (for group A: median 21 weeks, range 13-33, for group B: median 22 weeks, range 13-29, p=0.809) (Figure 1).

Quality of life ascertainment: A decreasing trend was observed in the QLQ-C30 score during the follow up for both groups of patients.

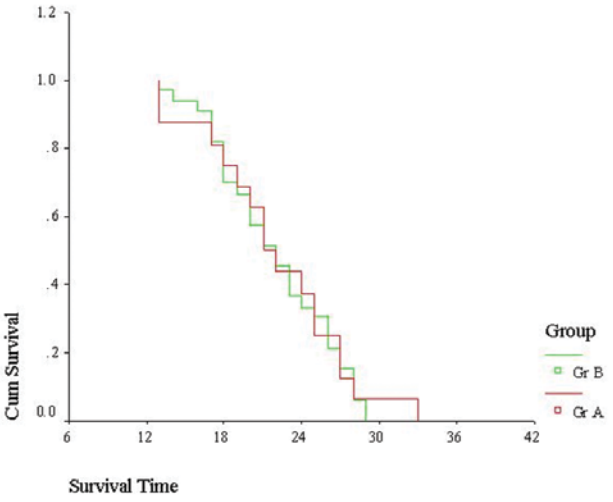

Figure 1. Survival time (in weeks) of the two study groups.

During the first month of the follow up period, group A presented a significantly higher score in the QLQ-C30 questionnaire than group B (p=0.028) mainly in items related with the emotional, cognitive and social functioning.

From the second until the fourth month there was no statistically significant difference in the QLQ-C30 score between the two studied groups of patients (p=0.444, p=0.484 and p=0.195 respectively).

The fifth and the sixth month, patients of group B presented significantly higher values of the QLQ-C30 score as compared with those of group A (p=0.010 and p=0.0003 respectively) mainly in items related with the physical and role functioning and also with the global health (Figure 2).

There is no satisfactory volume of data on the QoL of patients after the first 6 months of follow up, due to the great number of «fatal events». Thus statistical analysis of the QLQ-C30 questionnaire was based on the data of the first 24 weeks.

The average follow up score was calculated for each patient. According to the average QLQ-C30 score of each patient for all the weeks of follow up, group B patients had overall statistically significant higher values than group A (p=0.0001).

Hematological toxicity: All patients received at least one dose of gemcitabine and were therefore vulnerable to toxicity. Therapy was generally well tolerated and no treatment related to death or permanent discontinuation of the drug administration due to toxicity had occurred.

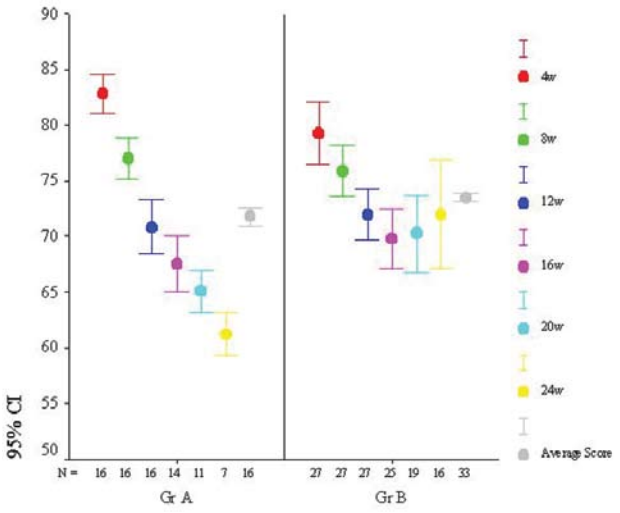

Figure 2. Quality of life of the two study groups.

Leucocytopenia, grade 1,2 and neutropenia, grade 1,2 were the most common severe toxic hematological side effects and were noted in 13 out of 16 (81.25%) and in 11 out of 16 (68.75%) patients respectively.

Neutropenic fever, concomitant with grade 3 or 4 neutropenia, was not observed. Anemia was noted in 5 cases (31.25%) and a mild thrombocytopenia in 9 patients (56.25%). A significant decrease of platelet count was noted in a patient during the seventh week of gemcitabine administration.

Due to hematological toxicity, treatment was discontinued temporarily in 6 cases and a total of 8 gemcitabine missing doses were noted.

Placement of plastic biliary stent: During the follow up period serum bilirubin levels of patients from both groups were almost within normal range (<4 mg/dl). Thus, placement of a second, plastic, biliary stent was not necessary.

DISCUSSION

For patients with unresectable PC, palliation must be directed toward relief of biliary obstruction, gastric outlet obstruction and intractable pain.[10] Although surgery offers the only change for long term palliation of these symptoms, it should be performed only in patients who are expected to live for more than a few months.[3]

Patients rarely present duodenal obstruction by the tumor at initial exploration and only 10-15% will develop it before they die.[11] Long-acting opioid analgesics can provide adequate pain control and appear to be best suited for such treatment.[6,9] The remaining major symptom of the disease, obstructive jaundice, can be resolved successfully with biliary drainage, since surgical bypass is associated with increased morbidity and mortality rates as well as longer hospital stay; endoscopic placement of a biliary endoprosthesis has become the method of choice as compared with surgery or percutaneous drainage.[6,12,13]

The superiority of metal over plastic stents has been proved by several randomized studies.[4,14] This resulted in improvement in both patient quality of life and long-term costs.[7,15,16]

Although some patients with PC who show jaundice as an initial symptom have a small tumor, which can be irradied, the vast majority of pancreatic cancers are in advanced stage at time of diagnosis.[17] On the other hand radiation therapy alone does not effectively treat patients with locally advanced disease outside of palliation.[18] All patients from our study were presented with locally advanced disease, no pain and jaundice.

In the present study biliary drainage with covered metallic endoprosthesis was successful and without any complications in all cases. The placement of a second plastic biliary stent through the metal covered endoprostheses, due to occlusion or additional endoscopic procedures were not needed.

Gemcitabine, a deoxycytidine analogue of arabinosycytosine, is one of the most promising new chemotherapeutic agents and have been associated with a survival benefit and an improvement of quality of life in patients with advanced PC.[19,20]

Although gemcitabine is considered as the «standard» care for these patients, several authors have reported a modest survival benefit compared to 5-FU.[21,22] Combination of gemcitabine with radiation therapy increases toxicity rates and does not significant impact survival rates compared with radiation and 5-FU.[23] Based on these controversial data, palliative care (antidepressants, nutritional supplements, analgesics, celiac plexus neurolysis, biliary decompression, pancreatic enzymes etc) remain the cornerstone of standard care for the vast majority of patients with advanced PC.[18]

In our study no statistically significant difference in survival between the two studied groups was observed (p=0.809). Gemcitabine did not achieve higher survival rates than symptomatic treatment in patients that had undergone endoscopical placement of a metal covered stent.

Some reasons for the relatively poor median survival time of gemcitabine group in the present study as compared with subgroups analysis of other prospective clinical trials that used the same drug in patients with advanced PC[24-26] can be the small number of our patients and differences of performance status.[27] On the other hand, based on observational studies, the median survival time for these patients range between 6 and 10 months.[28]

One decade after the pivotal trial comparing 5-FU with gemcitabine, numerous prospective, randomized trials have been conducted with newer agents such as cisplatin, irinotecan, oxaliplatin and capecitabine, alone or combined with gemcitabine, but a significant survival advantage was not demonstrated.[29-35] The first agent that has shown a statistically significant, but clinically modest survival benefit (two weeks only) for patients with advanced PC is the EGFR TKI erlotinib.[36,37] No randomized controlled trials of gemcitabine versus best supportive care were located.[38]

PC is a serious disease with a profound impact on QoL. Severe pain, jaundice, weight loss, poor appetite, general GI problems, vomiting and diabetes are common symptoms. The role of chemotherapy in PC and its impact on QoL is not very clear. The assessment of QoL is difficult and often inaccurate for several reasons.[22] Concerning the gemcitabine administration in patients with advanced PC, there is not any adequate number of randomised controlled trials to confirm some QoL benefits. The few open-design studies that have explored the influence of the drug on symptom relief/QoL indicate that only a minority of the patients may benefit.[21,23] Thus the improvement of QoL, using gemcitabine as palliative treatment in PC, remains open to question.

In our study a statistically significant difference was observed on the QLQ-C30 score (p=0.028) for the gemcitabine group during the first month of follow-up. This difference was not sustained later and was reversed on the fifth and sixth month (p=0.010 and p=0.0003 respectively). Also, according to the average QLQ-C30 score of each patient, the individuals that had undergone only endoprosthesis placement demonstrated statistically significant higher values (p=0.0001). Hematological toxicity and other side effects of gemcitabine are probably some of the reasons for these results. Due to hematological side effects, gemcitabine administration was discontinued temporarily in 6 out of 16 patients and a total of 8 missing doses was noted. Leucocytopenia, neutropenia and thrombocytopenia were observed in more than 50% of the subgroup that received gemcitabine and anemia at a rate of 31%.

The prevalence of these hematological side effects was expected and was similar with previous reports.[24]

In conclusion, gemcitabine administration didn't improve survival and QoL in patients with advanced pancreatic cancer previously treated with the placement of a covered metallic endoprosthesis due to obstructive jaundice.

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