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ORIGINAL ARTICLE

Gemcitabine as palliative treatment in patients with unresectable pancreatic cancer previously treated with placement of a covered metal stent. A randomized controlled trial

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Summary

Purpose: *To evaluate the efficacy of gemcitabine as palliative treatment in patients with advanced pancreatic cancer (PC) previously treated with placement of a covered metal biliary stent, taking into account survival and quality of life (QoL).*

Patients and methods: *Forty-nine patients with unresectable PC and obstructive jaundice, previously treated with the placement of a covered metal biliary endoprosthesis, were randomized to receive gemcitabine (group A: 9 males, 7 females) or to be followed without any anticancer intervention (group B: 18 males, 15 females). Gemcitabine was administered weekly as intravenous (i.v.) 30 min infusion of 1000 mg/m^2 for 3 consecutive weeks followed by 1-week rest (28-day cycle). QoL was evaluated with the QLQ-C30 questionnaire.*

Results: *229 gemcitabine doses were administered (median doses per patient 14.3, range 7-22). No statistically significant differences were observed regarding 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, group B patients showed statistically significant higher values (p=0.0001). Leukopenia, neutropenia, thrombocytopenia and anemia were the most common side effects in group A (81.25, 68.75, 62.50 and 31.25%, respectively).*

Conclusion: *Gemcitabine didn't show to improve survival and QoL in patients with advanced PC previously treated with a covered metallic biliary endoprosthesis due to obstructive jaundice.*

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

Introduction

PC is a common, highly lethal disease worldwide. 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 4-6 months.

Because of this dismal natural history, palliation remains the cornerstone of management of 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 hepatic dysfunction [4,5].

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Palliative relief of biliary obstruction 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 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 QoL 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 endoprosthesis due to obstructive jaundice.

Patients and methods

Inclusion criteria

Inclusion criteria for study entry were: written informed consent, age 25-75 years, diagnosis of PC confirmed either cytologically or histologically, locally advanced disease with no history of prior anticancer therapy and no indication for 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 function (normal blood urea and serum creatinine levels), satisfactory liver biochemistry after stenting (total bilirubin level $\leq$ 2-fold than the upper limit of normal, ALT and AST levels $\leq$ 2-fold than the upper limit of normal), INR $\leq$ 1.4, adequate bone marrow reserve (white blood cells/WBC/within normal limits, neutrophil count $\geq 2000/mm^3$, platelets/PLT/$\geq 100.000/mm^3$, hemoglobin/Hb/$\geq$ 10 g/dl) and no evidence of viral, autoimmune and hereditary liver disease.

Exclusion criteria

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, ineffective contraception for females of childbearing age and severe drug hypersensitivity.

Patient accrual

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

Stent insertion was carried out by means of endoscopic retrograde cholangiopancreatography (ERCP) using a therapeutic endoscope (Olympus TJF 140, Tokyo, Japan). The location and extent of the stenosis were determined by retrograde cholangiography. Before endoscopic biliary sphincterotomy, a guide wire was inserted through the stricture into the intrahepatic biliary system. The delivery catheter was then passed over the guide wire, and the stent was released under fluoroscopic control with endoscopic adjustment of the distal end if necessary. The position and functioning of the released stent were assessed by cholangiography.

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 2 study arms. For each patient on gemcitabine 2 control patients were selected. Sixteen patients (9 men and 7 women) received gemcitabine (group A) and 33 (18 men and 15 women) were followed up without any further treatment (group B) (p-value regarding sex distribution=1.00). The mean age of group A patients was 66.50 years (range 59-73) and of group B 66.58 years (range 58-73; p=0.95). The only intervention allowed for both groups was the placement of a plastic biliary endoprosthesis when occlusion of the metal stent occurred. Patients' allocation into the 2 arms was based on a sequence of random binary numbers (i.e. 111100111010…) that was developed in a computer-based program.

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.

Gemcitabine chemotherapy

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

Gemcitabine was administered as an i.v. 30 min infusion of 1000 mg/m^2 per week for 3 consecutive weeks followed by 1-week rest of each 28-day cycle.

Development of serious adverse effects and/or complications (hematological toxicity, renal failure, jaundice ≥ 4-fold than the upper limit of normal, grade 3 nausea/vomiting) and patient request to withdraw were reasons for removal from the study.

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

Study endpoints

Evaluation of survival in weeks between the 2 groups was the primary endpoint of this study. Evaluation of QoL of patients in both groups, measured monthly with the use of the QLQ-C30 EORT questionnaire, was the secondary endpoint. The placement of a second plastic biliary stent and the hematological toxicity of gemcitabine (leukopenia, neutropenia) were also evaluated.

Statistical analysis

The Student's t-test was employed to investigate QLQ-C30 score differences between the two examined groups of patients in each visit.

Survival distribution curves were plotted according to Kaplan-Meier method and were compared by the log-rank test.

Results

Group A patients received a total of 229 doses of gemcitabine (median doses per patient 14.3; 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 general condition was very poor.

Survival

At the end of the follow up period we had only fatal events. No statistically significant difference was observed between the 2 studied groups regarding survival (group A: median 21 weeks, range 13-33; group B: median 22 weeks, range 13-29; p=0.809) (Figure 1).

Quality of life assessment

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

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 issues related with the emotional, cognitive and social functioning.

From the 2nd until the 4th month there was no statistically significant difference in the QLQ-C30 score between the 2 studied groups of patients (p=0.444, p=0.484 and p=0.195, respectively).

In the 5th and 6th month group B patients 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 issues related with the physical and role functioning and also with the global health (Figure 2).

Because no satisfactory volume of data on the QoL of patients after the first 6 months of follow up existed, statistical analysis of the QLQ-C30 question-

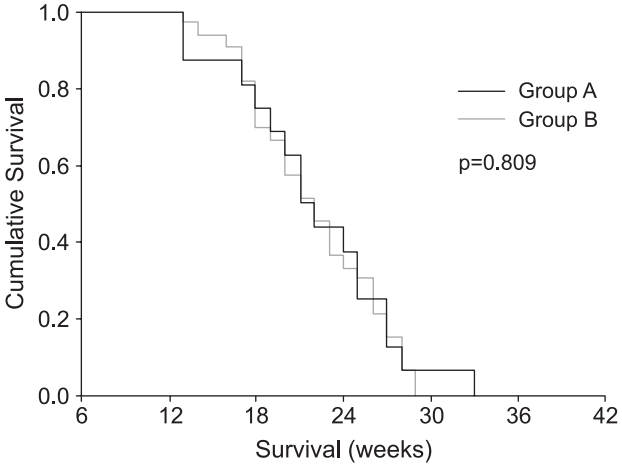

Figure 1. Survival of the two study groups.

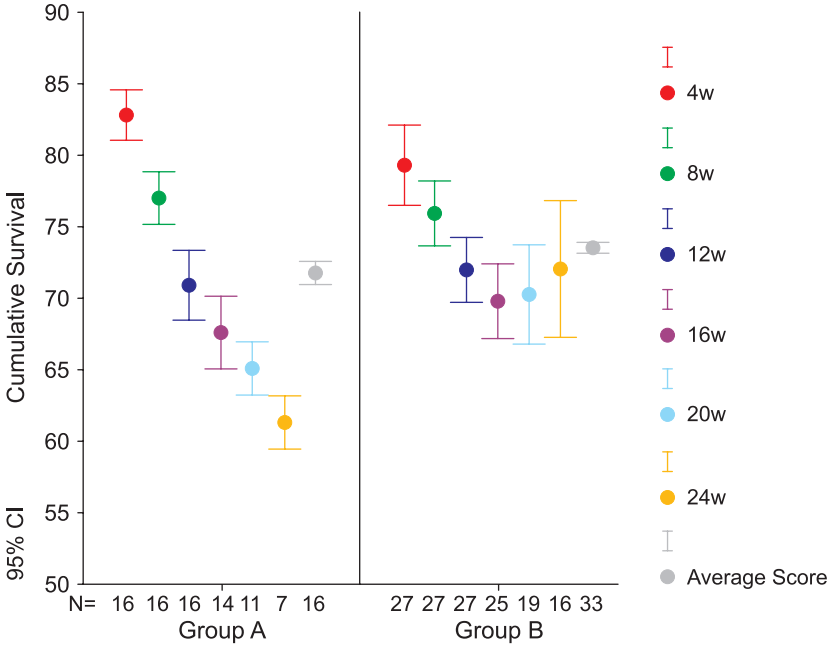

Figure 2. Quality of life of the two study groups. w=weeks.

naire was based on the data collected during 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 potentially subjected to toxicity. Therapy was generally well tolerated and no treatment-related death or permanent discontinuation of the drug administration due to toxicity occurred.

Grade 1 and 2 leukopenia and grade 1 and 2 neutropenia were the most common severe toxic hematological side effects and were registered in 13 out of 16 (81.25%) and in 11 out of 16 (68.75%) patients, respectively. No neutropenic fever occurred (Table 1).

Grade 2 and 3 anemia was noted in 5 (31.25%) cases and mild (grade 1 and 2) thrombocytopenia in 9 (56.25%) patients. A significant (grade 3) decrease of platelet count was noted in one patient during the 7th week of gemcitabine administration (Table 1).

Due to hematological toxicity (anemia grade 2 and 3 and thrombocytopenia grade 3), treatment was discontinued temporarily in 6 cases and a total of 8 gemcitabine missing doses were noted.

Table 1. Hematological toxicity for the gemcitabine group (group A)

Toxicity	*No. of patients*	*%*
Leukopenia (grade 1 and 2)	13	81.25
Neutropenia (grade 1 and 2)	11	68.75
Anemia (grade 2 and 3)	5	31.25
Thrombocytopenia (grade 1,2 and 3)	10	62.50
Febrile neutropenia	0	0.00

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 [9,10]. Although surgery offers the only chance 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 metallic over plastic stents has been proved by several randomized studies that revealed longer stent patency, minor occurrence of complications, less need for further intervention and shorter duration of hospital stay [4,14]. This resulted in improvement in both patient QoL 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 irradiated, the vast majority of PC cases are in advanced stage at the 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 of our study presented with locally advanced disease, with jaundice but without pain.

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 endoprosthesis due to occlusion, or additional endoscopic procedures were not needed. Thus, our results are in agreement with the studies reported above and also with the AGA recommendation for the palliation of patients with advanced PC, obstructive jaundice and life expectancy of more than several months [6].

Gemcitabine, a deoxycytidine analogue of arabinocytosine, is one of the most promising new chemotherapeutic agents and has been associated with a survival benefit and an improvement in QoL 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 significantly 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) remains 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 who had undergone endoscopic placement of a metal covered stent. Some reasons for the relatively poor median survival time of the gemcitabine group in the present study as compared with subgroups analyses 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 ranges between 6 and 10 months [28].

One decade after the pivotal trial comparing 5-FU with gemcitabine [21], 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 (2 weeks only) for patients with advanced PC is the EGFR tyrosine kinase inhibitor erlotinib [36,37]. No randomized controlled trials of gemcitabine vs. 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 gastrointestinal 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 [39]. Concerning gemcitabine administration in patients with advanced PC, no adequate number of randomized controlled trials to confirm some QoL benefits exists. The few open-design studies that have explored the influence of this drug on symptom relief/QoL indicate that only a minority of the patients may benefit [38,40]. Thus the improvement of QoL using gemcitabine as palliative treatment in PC remains open for discussion.

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 5th and 6th 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. Leukopenia, neutropenia and thrombocytopenia were observed in more than 50% of the patients of the subgroup that received gemcitabine and anemia occurred in 31% of the patients.

The prevalence of these hematological side effects was expected and was similar with previous reports [41].

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

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