Background and Objective: Gemcitabine is used as an effective drug for patients with advanced pancreatic cancer. Serum CA19-9 has been proven as the most sensitive and specific serum marker for pancreatic cancer. This study was to investigate the value of serum CA19-9 in evaluating treatment efficacy and predicting prognosis of patients with pancreatic cancer treated by gemcitabine-based chemotherapy. Methods: Seventy-one patients with histologically confirmed, locally advanced or metastatic pancreatic adenocarcinoma, whose Karnofsky’s performance status (KPS) score was ≥ 70 were treated with gemcitabine alone or with gemcitabine-based chemotherapy. CA19-9 was measured before and after chemotherapy. Results: Ten out of 71 patients had normal baseline CA19-9 levels, and 61 patients had increased baseline CA19-9 levels. The overall survival of patients were similar between the two groups, which were 9.0 months and 7.9 months, respectively (p = 0.797). The median baseline CA19-9 level for patients who had increased CA19-9 was (682 ± 558) U/mL before treatment. Patients whose pretreatment CA19-9 levels were < 682 U/mL achieved better survival than those whose pretreatment CA19-9 levels were ≥ 682 U/mL (9.6 months vs. 5.1 months, p = 0.001). In addition, patients with a pretreatment CA19-9 level of < 682 U/mL had a better tumor response (43.5% vs. 15.8%, p = 0.051) and clinical benefit response (48.1% vs. 29.2%, p = 0.125) than those whose pretreatment CA19-9 level was < 682 U/mL, but the differences were not significant. Patients with a fall of ≥ 25% in the baseline CA19-9 level after chemotherapy achieved a longer median overall survival (10.2 months vs. 5.0 months, p < 0.001), better tumor response (47.8% vs. 10.5%, p = 0.002) and better clinical benefit response (69.2% vs. 8.0%, p = 0.000) than those without a decrease of baseline CA19-9 or with a fall of < 25%. Multivariate analysis revealed that the baseline CA19-9 level before chemotherapy, decreased percentage of the CA19-9 level after chemotherapy, and the differentiation degree of tumor cells were independent risk factors for patients whose baseline CA19-9 levels were increased. Conclusion: The level of pretreatment base-line CA19-9 and the decreased percentage of baseline CA19-9 after chemotherapy are of predictive values for survival of patients with advanced pancreatic cancer undergoing gemcitabine-based chemotherapy and with an increased level of baseline CA19-9.

Pancreatic cancer is one of the most common malignances in China, with an increasing incidence rate in recent years. It often has latent onset and is seldom accompanied with specific symptoms and body signs. Once diagnosed, less than 20% of these patients have surgical opportunity. Even if radical surgical resection is performed, the recurrence and metastatic rates remain as high as 85%. For locally advanced, recurrent, and metastatic pancreatic cancer, gemcitabine monotherapy is the standard front-line chemotherapy. However the median survival of patients receiving this regimen is only 5 to 10 months. Serum carbohydrate antigen 19-9 (CA19-9) is a tumor-associated antigen which has been shown to be a highly specific and sensitive serum marker for pancreatic cancer, thus it is recommended for the diagnosis, staging, and postoperative surveillance of patients with pancreatic cancer. A few studies showed that the level of serum CA19-9 could predict the survival for patient with advanced pancreatic cancer undergoing systemic chemotherapy, although the results are disparate. This study was to determine the value of serum CA19-9 in evaluating therapeutic efficacy and predicting prognosis in pancreatic cancer treated with gemcitabine-based regimens.

Patients and Methods

Study subjects. A total of 71 patients with unresectable or metastatic pancreatic adenocarcinoma treated at Sun-Yet Sun University Cancer Center from January 2000 to January 2008 were enrolled. All patients met the following criteria: 1) Pathologically confirmed pancreatic cancer; 2) No history of previous treatment and
receiving first-line gemcitabine based chemotherapy; 3) Karnofsky performers status (KPS) score ≥ 70; 4) Dynamic measurement of serum CA19-9 before and after chemotherapy; 5) No jaundice. The median age of patients was 55 years (40–79 years). Forty-seven patients were males and 24 were females.

The primary tumor was located in pancreatic head in 21 cases, in pancreatic body and tail in 49 cases, and in the whole pancreas in one patient. Thirteen patients had locally advanced disease, and 58 patients had evidence of metastatic disease. The most common metastatic site was liver (55 cases), followed by posterior peritoneal lymph nodes and lung. Twelve cases were treated with gemcitabine monotherapy, 35 cases with gemcitabine plus oxaliplatin, 16 cases with gemcitabine plus 5-FU/CF in bolus, and the rest eight cases with gemcitabine plus capcitabine or docetaxel. The accumulated dosage for gemcitabine was 5.3 g/m² (2–16g/m²).

Measurement of serum CA19-9. Serum CA19-9 was measured one week before starting chemotherapy (baseline level) and every 3–4 weeks after each cycle of chemotherapy. The concentration of CA19-9 was measured by commercially available enzyme immunoassay (Electrochemiluminescenceimmunoassay, Elecsys 1010, Roche Diagnostics GmbH, Mannheim, Germany). The normal value of CA19-9 was < 35 U/mL, and the detectable range was from 0.6 to 500,000 U/mL.

Evaluation standard for therapeutic effects. Overall survival (OS). OS was defined as the time from beginning of the treatment until the date of death.

Objective remission rate (ORR). The Response Evaluation Criteria in Solid Tumors (RECIST) was used to determine the therapeutic effect. Complete remission (CR) was defined as complete disappearance of all target lesions without occurrence of new lesions, a decrease in the level of tumor markers to the normal level which was maintained for four weeks. Partial remission (PR) was defined as a decrease in the sum of the longest lengths of all baseline target lesions ≥ 30% which was maintained for four weeks. Stable disease (SD) was defined as a decrease in the sum of the longest lengths of all baseline target lesions less than PR, or enlargement of the lesions without progression. Progressive disease (PD) was defined as an increase in the sum of the longest lengths of the detected smallest target lesion ≥ 20%, or occurrence of one or more new lesion sites.

Clinical benefit response (CBR). CBR is a comprehensive assessment for cancer related pain, body strength, and weight. The standard is as the followings: 1) Improvement of at least one of the three indices, a. a decrease in the dosage of the painkiller by more than 50% compared with that given upon admission for more than four weeks without worsening any of them, b. reduction of pain severity for more than 50%, c. improvement of KPS score by more than 20 points; 2) Stable assessment scores for painkiller, pain, and body status, increase of more than 7% body weight for more than four weeks (exclusive of fluid retention).

Statistical analysis. Data were analyzed by SPSS 12.0 software. Quantitative data between two groups were compared using the R*C chi-square test. Comparison among multi-groups was performed using One-Way ANOVA analysis. Survival was analyzed by the Kaplan-Meier test. The Cox model was used for multi-factorial analysis to screen out independent risk factors. p < 0.05 indicated statistical significance.

Results

Overall therapeutic effects. Until April 2008, 64 patients died and seven patients were still alive. The median OS was 7.1 months. The one- and two-year survival rates were 13.8% and 1.7%, respectively. Among 71 patients, 47 were evaluable, of which 14 patients achieved PR, 22 patients remained SD, and 11 patients had PD. The overall response rate (ORR) was 29.8% (14/47). Fifty-nine patients were able to be evaluated for clinical benefit and the total CBR rate was 39.0% (23/59).

The relationship between serum CA19-9 and OS. Influence of the base-line CA19-9 level on OS. The base-line serum CA19-9 level was measured in all 71 patients one week before starting chemotherapy. Ten cases (14.1%) had normal base-line CA19-9 levels, while 61 cases (85.9%) had increased base-line CA19-9 levels. The median survival was 9.0 months for 10 patients with normal base-line CA19-9 levels and 7.9 months for 61 patients with increased base-line CA19-9 levels (p = 0.797) (Fig. 1A).

Sixty-one patients with elevated CA19-9 levels were further divided into Group A (33 cases) whose base-line CA 19-9 levels were below the medium value (682 U/mL) and Group B (28 cases) whose base-line CA 19-9 concentrations were above the medium value. The OS was longer for patients in Group A (9.6 months) than in Group B (5.1 months) (p = 0.001) (Fig. 1B).
Prognostic value of serum CA19-9 in patients with advanced pancreatic cancer receiving gemcitabine based chemotherapy

Influence of changes in postchemotherapy serum CA19-9 levels on OS. Postchemotherapy serum CA19-9 levels of all the 71 patients were measured every three to four weeks after each cycle of chemotherapy. Serum CA19-9 levels of 10 patients with normal baseline CA19-9 concentrations were maintained within normal ranges after chemotherapy, while those of 61 patients with increased baseline CA19-9 levels showed different extents of changes after chemotherapy. The postchemotherapy decline rate of CA19-9 was calculated as follows: (serum baseline CA19-9 value–the lowest postchemotherapy serum CA19-9 value)/serum baseline CA19-9 value × 100%. As shown in Fig. 1C, when 25% decline in the postchemotherapy serum CA19-9 was set as the cut-off point, the median survival time of patients with a decline in postchemotherapy CA 19-9 ≥ 25% (Group C, 32 cases) was significantly longer than that of the patients with a decline in postchemotherapy CA 19-9 < 25% or without decline (group D, 29 cases) (10.2 months vs. 5.0 months) (p < 0.001).

**Table 2** Correlation of serum CA19-9 levels to tumor response, clinical benefit response (CBR)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>P--mRNA level</th>
<th>1-actin mRNA level</th>
<th>ΔCt</th>
<th>ΔΔCt</th>
<th>2^-ΔΔCt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>10</td>
<td>31.21±1.07</td>
<td>21.33±1.21</td>
<td>9.89±0.36</td>
<td>0.00±0.36</td>
<td>1.00</td>
</tr>
<tr>
<td>Benign</td>
<td>10</td>
<td>30.02±1.20</td>
<td>20.29±1.08</td>
<td>9.73±0.32</td>
<td>-0.16±0.32</td>
<td>0.85–1.39</td>
</tr>
<tr>
<td>NSCLC</td>
<td>26</td>
<td>29.69±1.68</td>
<td>22.73±5.23</td>
<td>6.95±2.18</td>
<td>-2.94±2.18</td>
<td>1.69–34.78</td>
</tr>
</tbody>
</table>

PR: partial remission; SD: stable disease; PD: progression of disease.

**Table 3** Cox regression analysis for prognostic markers of pancreatic cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CA19-9 level (Above vs. below median)</td>
<td>0.324</td>
<td>0.152–0.691</td>
<td>0.004</td>
</tr>
<tr>
<td>CA19-9 response (&lt;25% decline vs. ≥25% decline)</td>
<td>0.248</td>
<td>0.111–0.565</td>
<td>0.001</td>
</tr>
<tr>
<td>Tumor grade (Low vs. moderate or high grade)</td>
<td>0.126</td>
<td>0.039–0.408</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Discussion

Human pancreatic cancer is one of the most malignant diseases in the world with highly poor prognosis. Gemcitabine is supe-
ior to 5-FU in improving CBR and prolonging the survival. The National Comprehensive Cancer Network (NCCN) panel recommends gemcitabine monotherapy as the standard front-line therapy for patients with advanced pancreatic cancer. Gemcitabine in combination with potentially synergistic agents, such as cisplatin, oxaliplatin, capcitabine, irinotecan, or 5-FU, exerts higher response rates, more favorable time to progression and higher CBR than gemcitabine monotherapy, especially for patients with good performance status whose ORR (CR + PR) is around 10% to 30%, tumor control rate is around 25% to 74%, and CBR is around 30% to 40%. In our study, most patients (83.1%) received gemcitabine based doublets. In accordance to previous studies, the objective effectiveness in our study was 29.8%; medium survival time was 7.1 months; one- and two-year survival rates were 13.8% and 1.7%, respectively.

CA19-9 is a sialylated Lewis blood group antigen targeted by the monoclonal antibody 1116 NS19-9 with the molecular weight of 5 x 10^3 ku. The concentration of CA 19-9 is increased in more than 80% of patients with advanced pancreatic cancer. However, patients who are genotypically negative for the Lewis blood group antigen, will not express CA19-9 even in the presence of active pancreatic cancer. About 7–10% of the general population is negative for this antigen and, thus, will not express CA 19-9. In this study, 10 of 71 patients (14.1%) had normal ranges of CA19-9 levels, whose overall survival was not significantly different from those with elevated CA19-9 levels, consistent with that reported by Halm et al. We believe that serum CA19-9 could not be used as a prognostic factor for those patient with normal baseline CA19-9 levels.

Maisey et al. conducted a retrospective study and found that the base-line CA19-9 level prior to chemotherapy was an independent predictive factor for survival of patients with advanced pancreatic cancer. Patients whose baseline CA19-9 was lowered than the average value achieved a higher one-year survival rate than those whose baseline CA19-9 was above the average. Ko et al. proved a positive correlation between the percentage of decline in postchemotherapy CA19-9 and the overall survival of patient with advanced pancreatic cancer. Halm et al. reported the survival of 43 consecutive patients with advanced pancreatic cancer treated with single-agent gemcitabine and revealed that a fall of at least 20% in the CA19-9 level following the start of chemotherapy was the only independent prognostic marker for OS. Park et al. conducted a phase II study and found that patients with a low level of baseline pretreatment CA19-9 (420 U/mL) showed a higher response rate than those whose baseline CA19-9 was above 420 U/mL. An important caveat in the interpretation of CA19-9 levels in pancreatic cancer is the presence of biliary obstruction, which results in the elevation of the marker level. In the current series, patients with jaundice or hyperbilirubinemia were excluded. Therefore this potential pitfall was avoided in the interpretation of baseline CA19-9 levels.

In conclusion, dynamic measurement of CA19-9 concentrations is a useful prognostic tool in predicting the survival of advanced pancreatic cancer patients with elevated serum CA19-9 levels receiving gemcitabine based chemotherapy.

References

Prognostic value of serum CA19-9 in patients with advanced pancreatic cancer receiving gemcitabine based chemotherapy


