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Elevated baseline CA19-9 levels correlate with adverse prognosis in patients with early- or advanced-stage pancreas cancer

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Abstract

CA19-9 is the most specific biomarker for pancreas cancer. We investigated the prognostic significance of normal (≤ 37 U/mL) versus elevated (>37 U/mL) CA19-9 levels in patients with resected and advanced pancreas cancer. Relevant data were obtained from patients treated for early-stage or advanced pancreatic adenocarcinoma at our institution. Log-rank tests were used to evaluate relationship between CA19-9 and clinical outcomes of interest for both early- and advanced-stage patients. A total of 123 patients were included (Group A: $N=30$ stage I/II; Group B: $N=93$ stage III/IV). In group A, elevated preoperative CA19-9 was significantly associated with lymph node involvement ($p=0.031$), tumor ≥ 3 cm ($p=0.011$), and lack of tumor differentiation ($p=0.048$). Failure of postoperative CA19-9 to normalize predicted significantly worse DFS ($p=0.021$). For group B, elevated baseline CA19-9 was associated with shorter OS on chemotherapy ($p=0.0008$) and decline in CA19-9 $>25\%$ with treatment was a significant predictor of improved OS ($p=0.0099$). Higher than normal CA19-9 level is an adverse prognostic factor in both early and advanced settings and may prove to be useful in the selection of patients for more aggressive therapy in future trials. CA19-9 level decrease of $>25\%$ predicts improved survival in advanced disease on chemotherapy.

Keywords

CA19-9; Pancreas cancer; Prognostic; Biomarker

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Conflict of interest None.

Introduction

Pancreas cancer remains the fourth leading cause of cancer death in the United States [1] and is most often detected in advanced stages where curative intervention is not possible. For patients with resected disease, adjuvant therapy improves median survival to 20–24 months [2–4]. Most patients with advanced-stage disease treated with standard gemcitabine-based therapies survive less than 7 months [5–13].

Carbohydrate 19-9 antigen (CA19-9) is the sialylated Lewis Le^a blood group antigen defined by the monoclonal antibody 1116 NS 19-9 [14]. While initially defined in colon cancer, CA19-9 is the most sensitive (80 %) and specific (90 %) biomarker for pancreas cancer [15] and is used as an adjunctive diagnostic and surveillance tool as well as in the assessment of response to therapy, in conjunction with radiographic studies. Approximately, 15–25 % of pancreas cancer patients will present with a normal CA19-9, and roughly, 5 % of the general population has a Lewis^{a-b}-genotype and therefore does not express CA19-9 [16].

In patients with early-stage disease, elevated preoperative CA19-9 is associated with higher disease stage [17], unresectability [18–20], and poor survival [21–26]. Failure of CA19-9 levels to decline below a certain threshold (from 111 to 200 U/mL) [17, 26, 27] or to normalize [18, 23, 28, 29] postoperatively is associated with inferior survival. In patients with advanced disease, elevated baseline CA19-9 and failure of CA19-9 to decline with therapy correlate with adverse outcomes [30–36].

Despite the available evidence, CA19-9 is not a routinely used as a stratification factor in clinical trials, and the utility of CA19-9 to independently guide clinical decision-making is not well established. We investigated the role of CA19-9 as a predictive and prognostic biomarker in patients with resected and advanced pancreas cancer.

Materials and methods

Design

This was a retrospective analysis of patients who were treated for pancreas cancer at the Ohio State University Medical Center from August 2003 to August 2008. Demographic data, pathologic data from resection specimens, CA19-9 levels, type of treatment, and outcome measures including progression and survival were obtained from a patient database. Tumors were staged based on the American Joint Committee on Cancer (AJCC)/TNM staging system. A CA19-9 radioimmunoassay kit is standardly used by our institution to determine CA19-9 levels. The manufacturer's recommended upper limit of normal value is 37 U/mL. For patients with resected disease, preoperative and postoperative CA19-9 values were obtained. For patients with advanced disease, baseline and serial CA19-9 values were collected. CA19-9 levels were measured within 4 weeks prior to or following therapy. The Ohio State University Institutional Review Board approved this study.

Eligibility

Eligible patients were required to have a cytologic or pathologic diagnosis of pancreatic adenocarcinoma that was resected (early-stage disease) or treated with systemic therapy (advanced-stage disease). Patients without postoperative level (early-stage), baseline level (advanced-stage) or at least one follow-up level were excluded.

Statistical analysis

Patient demographics were summarized using descriptive statistics. Institutional normal CA19-9 is defined as ≤ 37 U/mL. Elevated CA19-9 is defined as any level >37 U/mL. OS was determined from the date initial therapy to death from any cause, or censored at the date of last observation for patient still alive at the time of analysis. DFS was defined as the time from surgery to recurrence of disease, documented by radiographic imaging, death, or censored at last follow-up.

For patients with resected disease, postoperative CA19-9 level (normal vs. elevated) was correlated with overall survival (OS) and disease-free survival (DFS). The survival curves were compared using the log-rank test. Preoperative CA19-9 (normal versus elevated), when available, was correlated with lymph node status (positive or negative), tumor size (<3 cm or ≥ 3 cm), and tumor differentiation (well vs. moderate to poorly differentiated), all of which were determined on pathologic review of the resection specimen, as well as OS. Fisher's exact tests were used to examine the predictive effect of preoperative CA19-9 level on lymph node status (negative vs. positive), tumor size (<3 vs. ≥ 3 cm), tumor differentiation (well vs. moderate to poorly differentiated) and log-rank tests were used to examine the predictive effect of preoperative CA19-9 level on OS and DFS.

For patients with advanced disease, baseline CA19-9 level (normal vs. elevated) and decline in CA19-9 (0–25 vs. >25 % and 0–50 vs. >50 %) were correlated with OS. Actuarial survival curves were estimated using the method of Kaplan–Meier. Patients were subcategorized according to elevated or normal level of CA19-9 prior to treatment and the curves were compared by the log-rank test. Patients with advanced disease were also subcategorized according to maximum decrease in CA19-9 (>25 vs. ≤ 25 %, and >50 vs. ≤ 50 %) after treatment and the survival curves were compared by the log-rank test. Data were analyzed using the commercial statistical package SAS for Windows® Version 9.2 (SAS Institute Inc., Cary, NC, USA). *p* values of less than 0.05 were considered statistically significant.

Results

Patient demographics

Patient demographics are summarized in Table 1. A total of 123 patients (68 male and 55 female) with a median age of 59 years (range 37–85) were included in the analysis. Thirty patients (24 %) presented with early-stage (stage I or II) disease and had undergone surgical resection, and 93 patients (76 %) presented with advanced (stage III–IV) disease. Complete surgical pathology reports were available on 24 patients with resected disease. Forty-five percent had lymph node involvement, 73 % had tumors >3 cm in diameter, and 73 % had moderate to poorly differentiated tumors. Twenty-two (73 %) patients with resected disease received adjuvant therapy and 8 (27 %) received no therapy. Eighty-nine percent of patients with advanced disease received chemotherapy, 7 % received chemoradiotherapy, and 11 % received no therapy.

CA19-9 measurements

Preoperative CA19-9 levels were available from 24 of 30 patients with resected early-stage disease. Nine patients had normal levels (≤ 37 U/mL), and 15 patients had elevated levels (>37 U/mL) prior to surgery. Postoperative CA19-9 levels were available from all 30 patients. Thirteen patients had normal CA19-9 levels following surgery, and 17 patients had elevated CA19-9 levels. Pretreatment and serial CA19-9 levels were available for all 93 patients with advanced-stage disease. Seventy-six patients had elevated baseline CA19-9 levels and 17 patients had normal levels. For patients with advanced disease, 43 patients had

more than 25 % decrease in CA19-9 with gemcitabine-based therapy and 37 patients had a >50 % decrease, while 30 patients had 25 % decrease in CA19-9 levels and 36 patients had 50 % decline.

Survival analyses according to CA19-9

Early-stage disease—For patients with normal versus elevated preoperative CA19-9, median OS was 36 months (95 % CI 2.7, 36) versus 20 months (95 % CI 8, NA) ($p = 0.16$). At the time of analysis, two patients were still alive with follow-up intervals of 3 and 6 years. Data regarding the relationship between preoperative CA19-9 and pathologic prognostic factors is provided in Table 2. Elevated preoperative CA19-9 was significantly associated with lymph node involvement ($p = 0.031$), tumor size ≥ 3 cm ($p = 0.011$), and lack of differentiation ($p = 0.048$).

Kaplan–Meier curves for DFS according to postoperative CA19-9 level are provided in Fig. 1. Patients with normal postoperative CA19-9 had significantly improved median DFS of 16.5 months (95 % CI 5.7, NA) versus 7.6 months (95 % CI 3, 9.3) for patients with elevated CA19-9 ($p = 0.021$). Median OS for patients with normal versus elevated postoperative CA19-9 level was 36 months (95 % CI 11.3–36) versus 20 months (95 % CI 8–35.8) ($p = 0.27$).

Advanced disease—Kaplan–Meier estimation of overall survival according to baseline CA19-9 is provided in Fig. 2. Median OS was significantly improved at 32.3 months (95 % CI 18, NA) for patients with normal baseline CA19-9, versus 11.3 months (95 % CI 8.8, 16) for patients with elevated baseline CA19-9 ($p = 0.0008$).

Data regarding the relationship between decline in CA19-9 and overall survival are provided in Table 3. A significant survival benefit was observed for patients that had >25 or >50 % decline in CA19-9 with therapy as compared to patients with <25 or <50 % decline (16 vs. 7.8 months, $p = 0.0099$ and 16 vs. 8.5 months, $p = 0.0078$, respectively).

Discussion

The prognosis of pancreas cancer remains dismal with few advances made to improve outcomes in recent years. Although most patients with early-stage pancreas cancer will die of recurrent disease within 5 years, a small percentage of patients are able to achieve a cure or long-term survival [2]. Early identification of patients with more adverse prognosis is critical in order to develop more effective therapies to improve their chance of survival. The lack of data identifying predictive biomarkers and the limitations of radiographic assessment of response are barriers to successful treatment of this disease [37]. Furthermore, interpretation of cross-sectional imaging of pancreas cancer can be confounded by the significant inflammation, fibrosis, and desmoplasia that are frequently associated with these tumors [37], making response evaluation by RECIST criteria [38] difficult and potentially unreliable in the setting of advanced disease. Alternative means of response assessment could provide more effective risk stratification for advanced pancreas cancer patients in order to ensure effective therapy is provided.

In patients with resectable disease, we observed that normal preoperative CA19-9 levels were associated with a near doubling of overall survival compared to patients with elevated levels. Our results are consistent with other studies that suggest preoperative CA19-9 levels >37 U/mL [17, 21, 28, 29] or from at least 150 U/mL up to 1,000 U/mL depending on the study [17, 18, 24] predict inferior survival. We also investigated the association between elevated preoperative CA19-9 and known pathologic prognostic features. Our results suggest that elevated preoperative CA19-9 level is significantly associated with lymph node

involvement, tumors >3 cm, and moderate to poorly differentiated histology, all of which are adverse prognostic factors in resected pancreas cancer [39, 40]. Elevated preoperative CA19-9 > 37 U/mL was shown in only one other study to predict for lymph node involvement, advanced tumor stage (T3 or T4), and moderate to poor differentiation, as well as positive resection margin, another known adverse prognostic factor [28]. Other studies reported that elevated preoperative CA19-9 levels predict for lack of resectability (> 1,000 U/mL) [18] or for positive surgical resection margins [28]. Taken together these results suggest that elevated preoperative CA19-9 levels predict for pathologic features that are associated with unfavorable prognosis and may perhaps be useful in patient selection and stratification for clinical trials of neoadjuvant therapy in pancreas cancer.

Postoperatively in resected early-stage disease, our data suggest that failure of CA19-9 to normalize (> 37 U/mL) predicts inferior disease-free survival (DFS) compared with patients whose CA19-9 levels return to normal following surgery. Our study is only the second published evaluation of CA19-9 as a predictor of DFS in the postoperative setting. Another analysis of 40 patients showed that postresection normalization of CA19-9 translated into at least doubling of DFS as well [41]. This is a particularly relevant finding given the relevance of DFS in published and ongoing studies of adjuvant therapy in pancreas cancer [2]. As such, elevated postoperative CA19-9 levels can be considered for risk stratification in clinical trials or perhaps selection of patients for more aggressive therapies such as FOLFOX or FOLFIRINOX. Ultimately, this may lead to the development of more effective therapies for patients with poor prognosis.

Several other retrospective analyses of early-stage pancreas cancer have shown that failure of CA19-9 levels to decline to normal levels in the postoperative setting is associated with inferior overall survival (OS) [18, 23, 28, 29, 41]. Postresection CA19-9 level was also analyzed as a prognostic marker in the ESPAC-3 [4] and RTOG 97-04 [3, 27] phase III trials of adjuvant therapy in pancreas cancer. In both studies, persistent elevation of postoperative CA19-9 levels was significantly associated with inferior OS, although neither evaluated failure of CA19-9 to normalize. Interestingly, our survival analyses show that patients whose CA19-9 normalized postoperatively had OS very similar to patients with normal preoperative CA19-9. This finding suggests that normalization of CA19-9 following surgery may have a powerful prognostic indication.

Our results also confirm existing evidence that CA19-9 levels have both prognostic and possibly predictive value in the setting of advanced pancreas cancer. We show that advanced pancreas cancer patients with normal baseline CA19-9 levels have about a 3-fold survival advantage compared to those with elevated levels. Our study is the first to show that baseline elevated CA19-9 level is a significant adverse prognostic marker. We also demonstrate that CA19-9 levels decline of >25 % from baseline with treatment predicts for improved survival with therapy. These results are consistent with other published studies which show that declines of CA19-9 of at least 20 % and up to 75 % are associated with prolonged overall survival in patients receiving gemcitabine-based therapy [32–35]. Decrease in CA19-9 was also shown to be a strong predictor of objective radiographic response [34] in patients with advanced disease. Taken together, these data suggest that CA19-9 has prognostic and possibly predictive value and should be considered a stratification factor in clinical trials. Further prospective validation of CA19-9 levels, as a surrogate for radiographic response, is needed to confirm these findings.

Limitations to our study include the relatively small sample size, which limits its statistical power, and the retrospective design that introduces inherent bias, including selection bias and recall bias. Because of the retrospective nature of this analysis, patient treatment was not uniform or randomized in either the postoperative or the advanced setting. It is unlikely that

this influenced our results as the majority of patients in both groups received some form of chemotherapy or chemoradiotherapy that was consistent with established standard of care. Another potential limitation to our study is that biliary obstruction can confound the results. Although we did not have bilirubin measurements available on every patient, biliary decompression is routinely performed at our institution prior to treatment, which makes this effect unlikely.

In conclusion, our data show that elevation of CA19-9 above normal is an adverse prognostic factor in early- and advanced-stage pancreas cancer. Future clinical trials in pancreas cancer should consider using CA19-9 values above normal in patient selection and stratification. In the advanced setting, CA19-9 levels higher than normal may prompt a more aggressive course of therapy. CA19-9 levels decrease of >25 % predicts for improved survival in patients with advanced disease receiving therapy. In the early-stage setting, patients whose CA19-9 does not normalize following surgery should be considered for more aggressive adjuvant therapies on clinical trials. Also patients with elevated CA19-9 levels prior to resection should perhaps be considered for neoadjuvant therapy. Future prospective investigation of decline in CA19-9 may also serve as a surrogate for radiographic response.

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Fig. 1.
Kaplan–Meier estimation of disease-free survival in early-stage patients by postoperative CA19-9 value of >37 vs. $\leq$ 37 U/mL

Fig. 2.
Kaplan-Meier estimation of overall survival in advanced-stage disease by baseline CA19-9 value of >37 vs. ≤ 37 U/mL

Table 1**Patient demographics**

Characteristics	N (%)
Age (years)	
Median (range)	59 (37–85)
Sex	
M	68 (55)
F	55 (45)
Stage at diagnosis	
I–II	30 (24)
III	26 (21)
IV	67 (55)
Preoperative CA19-9 (early-stage only, N= 24)	
Normal (< 37)	9 (38)
Elevated (>37)	15 (62)
Postoperative CA19-9 (early-stage only, N= 30)	
Normal (< 37)	13 (43)
Elevated (>37)	17 (57)
Pathologic data (early-stage only, N= 22)	
Lymph nodes	
Negative	12 (55)
Positive	10 (45)
Tumor size	
<3 cm	6 (27)
≥ 3 cm	16 (73)
Differentiation	
Well-differentiated	6 (27)
Moderate to poorly differentiated	16 (73)
Baseline CA19-9 (advanced-stage only, N= 93)	
Normal (< 37)	17 (18)
Elevated (>37)	76 (82)
Adjuvant therapy	22 (73)
Chemotherapy	13 (43)
Gemcitabine-based	11 (85)
Other	2 (15)
Chemoradiotherapy	9 (30)
Gemcitabine-based	2 (22)
Fluoropyrimidine-based	7 (78)
No therapy	8 (27)
Palliative therapy	83 (89)
Chemotherapy	76 (92)
Gemcitabine-based	71 (93)

Characteristics	N (%)
Other	4 (7)
Chemoradiotherapy	7 (8)
No therapy	10 (11)

Table 2Relationship between preoperative CA19-9 and prognostic variables for early-stage patients ($N = 24$)

Variables	% of patients (early-stage disease)		<i>p</i>
	CA19-9 >37 U/mL (<i>N</i> = 15) (%)	CA19-9 ≤ 37 U/mL (<i>N</i> = 9) (%)	
Lymph node involvement	64	13	0.031
Tumor ≥ 3 cm	93	38	0.011
Moderate to poorly differentiated tumor	92	50	0.048

Six patients did not have complete pathology report or preoperative CA19-9 available

Table 3Overall survival in advanced disease patients by maximum percentage decline in CA19-9 ($N = 93$)

Change in CA19-9	No. of patients	Median OS (m)
0–25 % decline	30	16 (95 % CI 10.5–23)
>25 % decline	43	7.8 (95 % CI 4–11)
<i>p</i> value	–	0.0099
0–50 % decline	37	16 (95 % CI 12–23)
>50 % decline	36	8.5 (95 % CI 5–11)
<i>p</i> value	–	0.0078