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CLINICAL INVESTIGATION **Pancreas**

CA 19-9 AS A PREDICTOR FOR RESPONSE AND SURVIVAL IN ADVANCED PANCREATIC CANCER PATIENTS TREATED WITH CHEMORADIOTHERAPY

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Purpose: To investigate the significance of carbohydrate antigen 19-9 (CA 19-9) levels for predicting response and survival in pancreatic cancer (PC) treated with concurrent chemoradiotherapy.
Methods and Materials: We retrospectively reviewed data from 69 patients with PC between 1999 and 2005. All patients had elevated CA 19-9 levels before treatment. CA 19-9 levels (pre- and posttreatment CA 19-9) and their decline were analyzed for radiologic response and overall survival.
Results: Seventeen patients (25%) had a 50% or greater reduction in tumor size within 3 months of chemoradiotherapy (1 complete response, 16 partial responses). CA 19-9 decline was significantly correlated with radiologic response ($p = 0.03$). The median survival time (MST) was 12 months (range, 4–48 months), and 1-year survival rate was 44%. Pretreatment CA 19-9 > 1,200 U/mL (MST, 13 vs. 8 months; $p = 0.002$), posttreatment CA 19-9 >100 U/mL (MST, 17 vs. 10 months; $p = 0.0003$), and CA 19-9 decline ≤40% (MST, 13 vs. 10 months; $p = 0.005$) were the strongest and most unfavorable prognostic factors. In addition, patients with multiple unfavorable CA 19-9 levels had significantly worse outcomes than those without.
Conclusions: CA 19-9 decline shows a correlation with radiologic response. The combination of pretreatment CA 19-9 >1,200 U/mL, posttreatment CA 19-9 >100 U/mL, and CA 19-9 decline ≤40% may possibly serve as a surrogate marker for poor survival in advanced PC receiving chemoradiotherapy. © 2009 Elsevier Inc.

Pancreatic cancer, CA 19-9, Chemoradiotherapy, Tumor response, Survival.

INTRODUCTION

CA 19-9 is a sialylated Lewis blood group antigen, defined by Koprowski *et al*. (1), and a radioimmunometric assay was developed by Del Villano *et al*. (2). Elevated serum CA 19-9 level is observed in approximately three-quarters of all patients with pancreatic cancer (PC) who are genotypically positive for the Lewis blood group antigen (3). Although false-positive findings can occur in other gastrointestinal malignancies and benign diseases associated with obstructive jaundice or cirrhosis, the overall sensitivity of the assay is approximately 80% and specificity is 90% for detecting PC using a cutoff point of 37 U/mL as the upper limit of normal (4).

CA 19-9 is the most clinically useful serologic marker to enhance the diagnostic accuracy of PC when used in combination with imaging tests. In addition, serial measurements of CA 19-9 are performed for the clinical course and prognosis and for monitoring patients as an indicator for therapeutic response (5, 6). It has been reported that persistent elevation or rise in serum CA 19-9 levels after treatment may be indicative of poor response and prognosis. Conversely, decrease in CA 19-9 level may be associated with favorable prognosis and good response to treatment (7–12). In patients with locally advanced unresectable pancreatic cancer treated with combined chemoradiotherapy, the significance of CA 19-9 levels as a predictive factor for response or prognosis has not been thoroughly investigated (13–17). Furthermore, in this setting, there are no convincing data showing which of the CA 19-9 levels are unique as a surrogate for therapeutic response and prognosis.

The goal of this study was to evaluate the predictive value of CA 19-9 levels as a response parameter complementary to conventional radiologic imaging and define its prognostic importance in locally advanced unresectable PC undergoing concurrent chemoradiotherapy with a conventional fractionation scheme. The first aim was to investigate whether CA 19-9 decline from pre- to posttreatment levels can predict radiologic response of the pancreatic mass. The second was to determine which degree of CA 19-9 levels (pretreatment CA 19-9, posttreatment CA 19-9, and CA 19-9 decline) would be most predictive of a favorable prognosis.

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Conflict of interest: none.

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METHODS AND MATERIALS

Patient selection

Between January 1999 and December 2005, a total of 127 consecutive patients with PC underwent concurrent chemoradiotherapy as a first treatment. After retrospective chart review with Institutional Review Board approval, 69 patients were included in this study. Eligibility criteria included elevated CA 19-9, histologically proven adenocarcinoma of the pancreas, unresectable (T4) or borderline resectable (T3) disease, no detected distant metastasis, no previous history of chemotherapy or radiotherapy, age between 15 and 75 years, Eastern Cooperative Oncology Group performance status of 0–2, and normal pretreatment blood counts and renal and liver function with the exception of hyperbilirubinemia.

Those with a normal range of CA 19-9 <37 U/mL (24 patients) or no data of CA 19-9 (9) were excluded. Patients were also excluded when they presented with distant metastasis at diagnosis (11) or at 1-month follow-up after treatment (8) and if they had not completed the planned radiotherapy (6) because of either disease progression or patient refusal. The pretreatment evaluation consisted of a complete medical history and physical examination, helical computed tomography (CT) scan of the abdomen, endoscopic ultrasonography, radiograph or CT of the chest, and routine blood counts and serum chemistry. A whole-body bone scan was obtained when indicated. Endoscopic retrograde cholangiopancreatography and bile drainage were performed for obstructive jaundice. All tumors were staged according to the American Joint Committee on Cancer Staging System (6th edition, 2002).

Treatment scheme

All patients underwent concurrent chemoradiotherapy with conventional fractionation. In the early period, two-dimensional radiotherapy was used in only 7 patients (10%). Most patients (90%) received three-dimensional conformal radiotherapy. Thirty patients (43%) received involved-field irradiation, which consisted of gross tumor volume and a generous margin (2 cm). Radiotherapy of the lymph node areas was undertaken in 39 patients (57%). In general, the field arrangement was the three-field technique, consisting of opposed laterals and an anteroposterior field or the four-field box technique. A total dose of 45 or 50.4 Gy was applied in daily fractions of 1.8 Gy, 5 days per week, using a 10 MV linear accelerator. In most patients (57 patients, 83%), gemcitabine-containing combination chemotherapy (1,000 mg/m^2 weekly) was given during a 5-week course of radiotherapy. Second, a paclitaxel-containing regimen was used in 10 patients (14%). After completion of concurrent chemoradiotherapy, 57 patients (83%) received maintenance chemotherapy until disease progression, treatment-limiting toxicity, or death. When the residual tumors became resectable during the follow-up period, which occurred in only 10 patients (14%), radical resection was performed. The time interval from chemoradiotherapy to surgery ranged from 4 to 6 months, depending on patient's general condition.

Determination of CA 19-9 level

Serum levels of CA 19-9 were determined using the enzyme-linked immunosorbent assay method (COBAS CORE II, Diagnostics Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland) in the earlier years. It was replaced by electrochemiluminescence immunoassay (Vitros ECiQ, Ortho-Clinical Diagnostics, Amersham, UK) in 2002. There is no difference in sensitivity between the two methods. Serum samples for CA 19-9 were obtained from all patients at 2 weeks before treatment, 1–3 months after treatment, and every 3–6 months during the follow-up period. The recommended upper limit of normal for CA 19-9 is 37 U/mL. To evaluate the correlation between radiologic response and level of CA 19-9, serum levels of CA 19-9 were obtained at 3-month follow-up.

Assessment of response and follow-up

During the course of radiotherapy, all patients were examined for the assessment and management of treatment related to toxicity at least once per week or more as needed. Patients were followed up every 2–4 weeks until acute radiation reaction subsided, and then every 3–6 months. Follow-up evaluation included medical history, physical examination, routine laboratory tests, and imaging studies. Response evaluation of the pancreatic tumor was evaluated by a dynamic CT scan 3 months after treatment using the Response Evaluation Criteria in Solid Tumors criteria (18).

Table 1. Patient demographics (n = 69)

Characteristics	n	(%)
Age (y)		
Median (range)	62	(37–74)
Gender		
Male	45	(65)
Female	24	(35)
Performance		
ECOG 0	1	(1)
ECOG 1	40	(58)
ECOG 2	28	(41)
Tumor location		
Head	53	(77)
Body	10	(14)
Tail	6	(9)
Tumor stage		
T3	8	(12)
T4	61	(88)
Lymph node		
N0	49	(71)
N1	20	(29)
Stage		
IIA	4	(6)
IIB	4	(6)
III	61	(88)
Radiotherapy dose (Gy)		
45	59	(86)
50.4	10	(14)
Concurrent chemotherapy		
Gemcitabine-based	57	(83)
Paclitaxel-based	10	(14)
Other	2	(3)
Maintenance chemotherapy		
No	12	(17)
Yes	57	(83)
Surgery after chemoradiotherapy		
Whipple	3	(4)
PPPD	6	(9)
Distal pancreatectomy	1	(1)
Pretreatment CA 19-9 (U/mL)		
Median (range)	567	(47.9–20000)
Posttreatment CA 19-9 (U/mL)		
Median (range)	153	(6.4–7350)
CA 19-9 decline (%)		
Median (range)	78	(-124–99)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PPPD = pylorus preserving pancreaticoduodenectomy.