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Assessing Prognosis in Metastatic Pancreatic Cancer by the Serum Tumor Marker CA 19-9: Pretreatment Levels or Kinetics during Chemotherapy?

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Key Words

Carbohydrate antigen 19-9 · Gemcitabine · Pancreatic cancer · Prognostic factor

Summary

Background: The carbohydrate antigen 19-9 (CA 19-9) is currently the most widely used serum tumor marker in pancreatic cancer (PC). CA 19-9 pretreatment levels as well as CA 19-9 kinetics during systemic chemotherapy can provide prognostic information regarding survival of patients with metastatic PC. **Case Reports:** We report the clinical course of 2 patients with metastatic PC who underwent palliative chemotherapy with gemcitabine. Both patients showed a significant elevation of pretreatment CA 19-9 levels (7,505 and 150,000 U/ml, respectively), however, subsequently they experienced a highly significant reduction (>90%) of CA 19-9 kinetics under gemcitabine chemotherapy. A good disease control and a clinical benefit response were achieved in both patients. Time to tumor progression was 30 weeks and 28 weeks, overall survival 14 months and 11 months, respectively. **Conclusion:** These data indicate that CA 19-9 kinetics under chemotherapy may possibly serve as a useful surrogate marker for time to tumor progression and survival in advanced PC.

Schlüsselwörter

Carbohydrat-Antigen 19-9 · Gemcitabin · Pankreaskarzinom · Prognostischer Faktor

Zusammenfassung

Hintergrund: Das Carbohydrat-Antigen 19-9 (CA 19-9) ist gegenwärtig der beim Pankreaskarzinom am häufigsten eingesetzte Tumormarker. Bei Patienten mit metastasiertem Pankreaskarzinom können sowohl anhand der prätherapeutischen CA-19-9-Spiegel als auch anhand der CA-19-9-Kinetik unter Chemotherapie prognostische Aussagen bezüglich des Überlebens getroffen werden. **Fallberichte:** Wir berichten über zwei Patienten mit metastasiertem Pankreaskarzinom, die im Rahmen einer palliativen Chemotherapie mit Gemcitabin behandelt wurden. Beide Patienten zeigten bei Therapiebeginn hochsignifikant erhöhte CA-19-9 Werte (7505 und 150 000 U/ml), unter Chemotherapie mit Gemcitabin kam es jedoch bei beiden Patienten zu einem deutlichen Abfall (>90%) in der CA-19-9-Kinetik. Bei beiden Patienten konnte eine gute Krankheitskontrolle sowie ein klinischer Benefit erreicht werden. Die Zeit bis zum Fortschreiten der Erkrankung betrug 30 bzw. 28 Wochen, das Gesamtüberleben lag bei 14 bzw. 11 Monaten. **Schlussfolgerung:** Diese Daten zeigen, dass die CA-19-9-Kinetik unter Chemotherapie möglicherweise als nützlicher Surrogatmarker für die Zeit bis zur Tumorprogression bzw. für das Überleben beim fortgeschrittenen Pankreaskarzinom fungieren kann.

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Introduction

Pancreatic cancer (PC) is the 4th most frequent cause of death from cancer in Germany, and the estimated annual incidence is about 12/100,000. Over the last decade, the incidence of PC in men was constant, whereas in women it increased over the last years [1]. Survival still remains poor with a 5-year survival rate of only 4% in all patients. In patients with an advanced stage of disease, single-agent gemcitabine (Gem) is regarded as the standard of care for the first-line chemotherapeutic treatment, based on its improvement in clinical benefit response and survival [2]. Known prognostic factors for survival in patients with advanced PC are stage of disease, degree of tumor cell differentiation, weight loss, performance status, and primary tumor site [3, 4]. Furthermore, also the serum tumor marker carbohydrate antigen 19-9 (CA 19-9) can provide prognostic information. CA 19-9 is a tumor-associated antigen (first described by Koprowski et al.) defined by a monoclonal antibody (1116 NS 19-9) which was produced by a hybridoma prepared from mouse spleen, immunized with a human colorectal carcinoma cell line [5, 6]. CA 19-9 is the sialylated Lewis (Le)^{a} blood group antigen, and individuals with a Le^{a-b-} phenotype (lacking the Lewis antigen glycosyltransferase) are unable to synthesize CA 19-9 [7]. In patients receiving systemic chemotherapy for advanced PC, pretreatment CA 19-9 levels were found to be a significant and also independent adverse prognostic factor for survival [8–10]. However, also a CA 19-9 decline ('CA 19-9 response') under chemotherapy may serve as predictor of survival [8, 11–17]. Nevertheless, there is no unique cut-off point defined for classifying a patient as a 'CA 19-9 responder' up to now. In order to separate patients with advanced PC into the two groups of 'CA 19-9 responder' and 'CA 19-9 nonresponder', most studies used a decline of pretreatment CA 19-9 levels of >20% or >50% after 8 weeks of treatment, respectively (table 1).

In this paper, we report the clinical course of two patients with metastatic PC who showed highly elevated CA 19-9 pretreatment values, but subsequently developed a strong CA 19-9 response under systemic chemotherapy with Gem. Based on these two cases, we furthermore discuss the question what clinical information CA 19-9 values can provide to assess prognosis in patients with advanced PC.

Table 1. Impact of CA 19-9 reduction in response to chemotherapy with gemcitabine on survival in patients with advanced PC

Author	CA 19-9 reduction, %	Median overall survival, months	
		Responder	Nonresponder
Halm et al., 2000 [13]	>20	8.9	3.7 ($p < 0.001$)
Saad et al., 2002 [8]	>50	13.8	8.0 ($p = 0.0272$)
Ziske et al., 2003 [15]	>20	12.8	8.1 ($p = 0.006$)
Ko et al., 2005 [17]	>25	9.61	4.64 ($p < 0.001$)
	>50	10.8	5.82 ($p < 0.001$)
	>75	12.0	6.0 ($p < 0.001$)

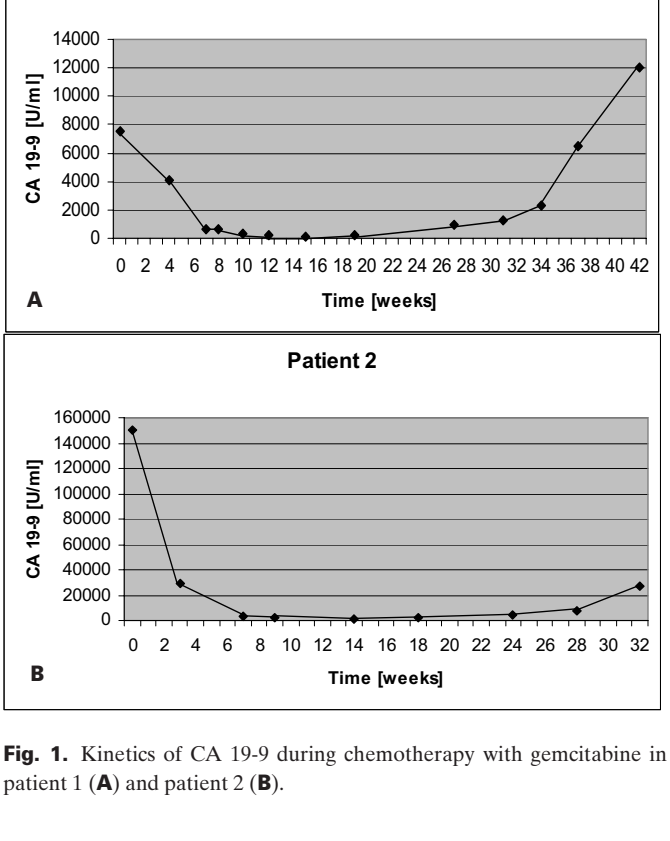

Fig. 1. Kinetics of CA 19-9 during chemotherapy with gemcitabine in patient 1 (**A**) and patient 2 (**B**).

Case Report

Case 1

A 46-year-old female with painless icterus was admitted to our hospital in August 2004. She had no particular past or family history. Physical examination revealed icteric conjunctiva, and laboratory studies found a total bilirubin level of 5.3 mg/dl at presentation. Imaging studies (abdominal ultrasound and CT scan) showed an extrahepatic cholestasis caused by a mass in the head of the pancreas with multiple synchronous liver metastases. After placement of a bile duct stent by endoscopic retrograde cholangiopancreatography (ERCP), a CT-guided biopsy of a liver lesion histologically revealed a poorly differentiated (G3) adenocarcinoma. At the beginning of a systemic chemotherapy with single-agent Gem, CA 19-9 values were found to be elevated with a pretreatment level of 7,505 U/ml (Elecsys®, Roche Diagnostics, Mannheim). The reference range was defined as levels <37.0 U/ml. At that time, the serum bilirubin level was within the reference range (1.1 mg/dl), and there were – also on imaging – no signs of cholestasis. CA 19-9 kinetics under chemotherapy of this patient are shown in figure 1A. After 8 weeks of Gem treatment, a CA 19-9 reduction of about 91% (672 U/ml) was observed. The CA 19-9 nadir was reached 15 weeks after treatment initiation with a level of 112 U/ml. During therapy the patient was doing well, no pain medication was required, body weight was stable, and Karnofsky performance status (KPS) was 90%. The bile duct stent was routinely replaced every 3 months with no further laboratory or imaging signs of extrahepatic cholestasis. According to the Response Evaluation Criteria in Solid Tumors (RECIST) the best response on imaging was stable disease, with no change in the diameter of the primary tumor in the pancreas and a nearly complete disappearance

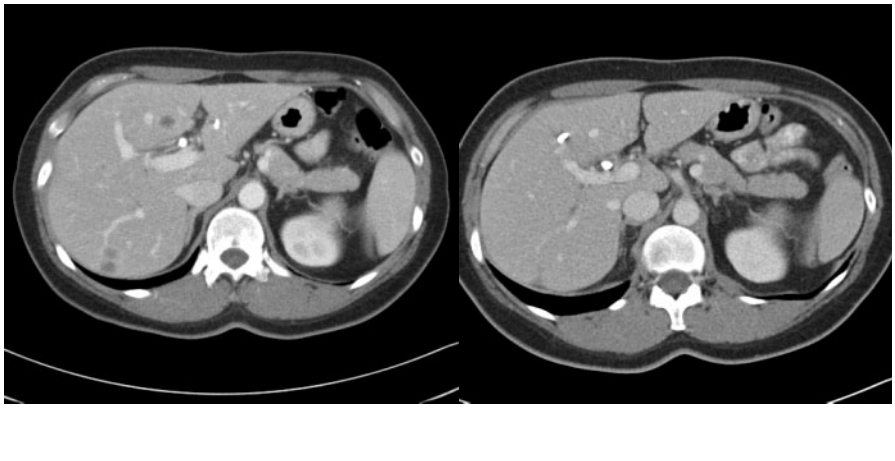

Fig. 2. Radiographic response to gemcitabine in an abdominal CT scan after 19 weeks of chemotherapy (patient 1): nearly complete disappearance of all hepatic lesions.

of all hepatic lesions (fig. 2). After 19 weeks a first rise in CA 19-9 levels was detected; a CT scan performed 30 weeks after the start of Gem confirmed hepatic tumor progression. The patient received further chemotherapy with capecitabine, Gem plus oxaliplatin (GemOx) and pemetrexed, but with none of these agents further disease stabilization could be achieved. The patient died due to disease progression in October 2005 (resulting in an overall survival of 14 months from initial diagnosis).

Case 2

A 73-year-old female was admitted to our department in July 2005 due to a consecutive weight loss and epigastric and back pain. There were no pathological findings in physical examination, the values of routine laboratory sampling (blood count, liver and renal function, coagulation) were within the normal range. An abdominal CT scan showed a tumor in the head of the pancreas with multiple hypodense liver lesions. Histology after CT-guided biopsy of a liver mass yielded the diagnosis of an intermediately to poorly differentiated ductal adenocarcinoma (G2-3). The patient was randomized to first-line chemotherapeutic treatment with oral capecitabine within a multicenter phase III trial. After two cycles of chemotherapy, an intensive increase of CA 19-9 values was detected (pretreatment CA 19-9 level: 27,177 U/ml; after two cycles of capecitabine: 150,000 U/ml) without any laboratory or imaging signs of cholestasis. A staging CT scan confirmed progression of hepatic metastases, and subsequently the therapy was switched (according to the study protocol) to single-agent Gem. CA 19-9 kinetics under second-line chemotherapy with Gem are summarized in figure 1B. After 8 weeks of chemotherapy, a strong CA 19-9 reduction of nearly 99% (2,092 U/ml) was observed. The CA 19-9 nadir was reached 14 weeks after treatment initiation with Gem with a level of 1,261 U/ml. Clinically the patient was doing well, an increase of KPS from 80% to 90% was observed. Best response on imaging – according to RECIST – was a partial remission documented in a CT scan 18 weeks after start of Gem. A hepatic tumor progression was detected in the CT scan performed 28 weeks after the start of single-agent Gem. The chemotherapy regimen was therefore again changed to oxaliplatin in combination with leucovorin-modulated 5-fluorouracil (as continuous infusion) in March 2006. After only one cycle of this salvage regimen, the patient again showed a disease progression and developed a malignant stenosis of the bile duct, which could not be controlled by ERCP-guided stenting or percutaneous drainage. The patient died due to a sepsis with *Enterococcus faecium* in May 2006 (11 months after first diagnosis of metastatic PC).

Discussion

CA 19-9 is currently the most widely used serum tumor marker in PC. For patients with advanced stages of disease there is evidence that not only the pretreatment levels of CA 19-9 can serve as prognostic factor, but also kinetics under chemotherapy can provide useful prognostic information regarding survival. Published data for the prognostic impact of CA 19-9 kinetics ('CA 19-9 response') in trials using single-agent Gem as palliative first-line treatment are summarized in table 1. Nevertheless there is, to date, no clinical trial that addressed the specific question which parameter would be the more useful one for identifying patients with a favorable prognosis: pretreatment CA 19-9 levels or CA 19-9 kinetics during chemotherapy.

Both patients reported in this paper had a highly elevated CA 19-9 level at treatment initiation with Gem. According to data published by Maisey et al. [9] and Saad et al. [8] the median overall survival in patients with pretreatment CA 19-9 levels >1,000 U/ml ranges between 5.5 and 7.4 months. However, as described above, our two patients experienced a strong and long-lasting CA 19-9 reduction under chemotherapy with single-agent Gem. This CA 19-9 decline correlated well with a significant prolongation of the time to tumor progression (defined by imaging criteria according to RECIST) of 30 weeks and 28 weeks, respectively. According to all published phase III trials that evaluated the role of chemotherapy in advanced PC, the median time to tumor progression with single-agent Gem ranges between only about 10 to 16 weeks [18, 19]. Our data also are comparable with the findings of Ko et al. [17] showing that a reduction of pretreatment CA 19-9 levels of more than 75% under a fixed dose rate Gem therapy is a strong prognostic factor yielding a prolonged median survival of about 12 months (table 1).

Based on our clinical observations reported in this paper, we would hypothesize that CA 19-9 kinetics under Gem chemotherapy may possibly serve as an even more useful prognostic parameter than the absolute pretreatment values of CA 19-9. Therefore we recommend, like other groups as well [9], further investigation of this issue in the setting of controlled clinical trials. Only if unique and standardized CA 19-9 measurements will be included in large randomized phase III trials, the value of their prognostic significance – regarding both pretreatment values and kinetics under chemotherapy – can be defined.

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