THE RELEVANCE OF SOME TUMORAL MARKERS IN PATIENTS WITH PANCREATIC CANCER

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Keywords: *pancreatic cancer, tumoral markers*.
Abstract: The pancreatic cancer is a disease with exponentially increased incidence, especially over the last decades, being the sixth or even fifth cause of death by cancer in most of the modern societies. Moreover, it is estimated that almost 95% of the patients with this disease are presenting to the doctor in the advanced and unresectable stages. Thus, the only way of establishing a diagnosis in the early stage, potentially curable, would be a rigorous anamnesis that would reveal the early symptoms to 'send' the patient to the doctor in the early stage. In this way, all hopes are turning to early diagnosis and/or the discovery of an effective therapeutic agent. Thus, in the present report we will be interested in presenting the relevance for the serum determination of some tumoral markers, such as CA19-9 (carbohydrate antigen 19-9) and CEA (carcinoembryonic antigen) in our selected patients with pancreatic cancer. In this way, our results are showing the relevance in determining these specific tumoral markers, especially as predictors for recurrences after pancreatic neoplasm surgery, since the determination of the serum level of CA 19-9 seem to be relevant in the cases when the antigen level drops immediately after the surgery, then increases progressively, highlighting the emergence of recurrence.

INTRODUCTION

Lately, the incidence of pancreatic neoplasm has increased steadily, especially over the last 4 decades in many parts of the world and has become the sixth or even fifth cause of death by cancer in the Western countries (Pezzilli et al., 2004). Moreover, in 2000 there were diagnosed 216.400 new cases and 215.500 deaths caused by this disease worldwide, while in 2004 in the United States there were predicted 31.860 new cases and 31.270 deaths, which indicate that, due to a very low survival rate, the incidence and mortality are almost similar (Tamm et al., 2003).

In this way, it is estimated that almost 95% of the patients with this disease are presenting to the doctor in the advanced and unresectable stages. In fact, over the past few decades the development and advance of the surgical methods and techniques have improved only morbidity and hospital postoperative mortality, without significant impact on survival. As mentioned, in specialized pancreatic surgery centers mortality is less than 5%. Also, long-term survival, for 5 years after resection of the R0 is reported fewer than 10% in literature per series of screened patients, with no record regarding the recurrence during this period (Kayahara et al., 1995).

In addition, most of the studies carried out have not been able to identify the significant risk factors for pancreatic cancer. Still, several risk factors were described as being involved: smoking, chronic pancreatitis, diabetes mellitus, previous gastrectomy and exposure to radiation or chemicals such as chlorinated hydrocarbon based solvents (Gold et al., 1998).

In this way, a serious disadvantage encountered in pancreatic cancer is the fact that diagnosis is established too late despite the development of new technologies, as the main symptoms, pain and jaundice appear later when the tumor is already locally and/or systemically advanced and therefore unresectable, making the prognosis extremely unfavorable.

Currently, the only way of establishing a diagnosis in the early stage, potentially curable, would be a rigorous anamnesis that would reveal the early symptoms to 'send' the patient to the doctor in the early stage.

Thus, as the current diagnostic means and techniques can not accurately assess all the pancreatic tumors and also considering that the evolution and improvement of various surgical techniques has reached a maximum, all hopes are turning to early diagnosis and/or the discovery of an effective therapeutic agent.

In this way, in the present report we will be interested in presenting the relevance for the serum determination of some tumoral markers, such as CA19-9 (carbohydrate antigen 19-9, also called cancer antigen 19-9 or sialylated Lewis antigen) (Perkins et al., 2003) and CEA (carcinoembryonic antigen) (Boehm et al., 2000), in our selected patients with pancreatic cancer.

MATERIAL AND METHODS

Seven patients were selected from the "Sf. Spiridon" University Hospital Iasi, Romania. The main inclusion criterion was represented by the presence of the pancreatic neoplasm. As mentioned, these were represented by CA19-9 (carbohydrate antigen 19-9) and CEA (carcinoembryonic antigen). Their determination was performed by using specifically commercial kits in the Hospital Laboratory.

In this way, the number value for CA19-9 is less then 34 U/mL, while in the case of ACE, the normal values are considered to be less then 5 ng/ml in non-smokers and also less then 10 ng/ml in smokers.
Also, it is important to mention that considering the low number of patients on which the determination of serum levels of CA19-9 and ACE tumoral markers could be performed, it was hard to advance a proper statistical processing to formulate very significant statistical conclusions. However, we think that our data is extremely relevant in demonstrating the importance of determining these markers for the patients with pancreatic cancer.

RESULTS

As previously mentioned, our study included seven patients, for which the antigen level was measured in the serum.
In this way, one patient with T3NxM0 cephalic neoplasm who underwent double bypass, ABD and GEA, had CA 19-9 of 1557 U/mL at 5 months and of 1212 U/mL at 6 months (Figure 1), while the CEA value at 5 months was 4.2 ng/mL and 4.8 ng/mL at 6 months. This patient died at 10 months after the prelevation.

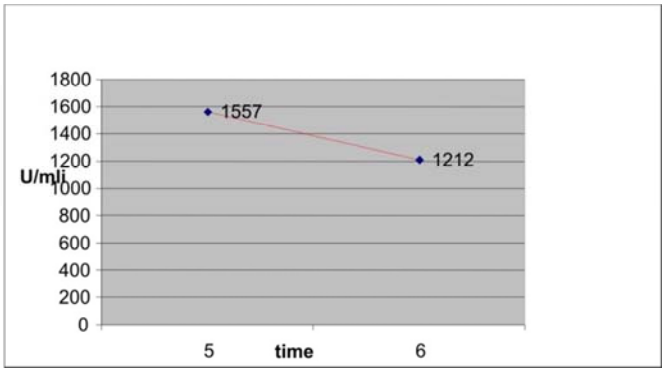

Figure 1. CA 19-9 at five and six months.

In the case of the second patient with cephalic TxNxM0 neoplasm undergoing DPC- Whipple R1, which survived 28 months, we observed that CA 19-9 levels were of 8000 U/mL at 15 months, 10000 U/mL at 20 months and 14789 U/mL at 27 months (Figure 2).

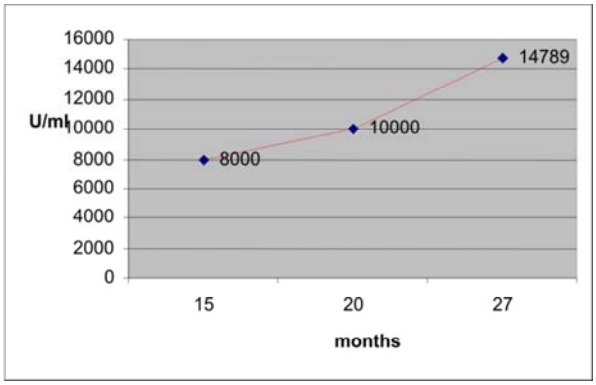

Figure 2. CA 19-9 at 15, 20 and 27 months.

Also, for the third patient with cephalic T2N0M0 neoplasm who underwent the DPC-Whipple R0 in 22.04.2002, and was still alive in October 2006, we could observe some CA 19-9 levels that varies from 214 U/mL at 18 months, 198 U/mL at 24 months, 160 U/mL at 30 months (Figure 3).

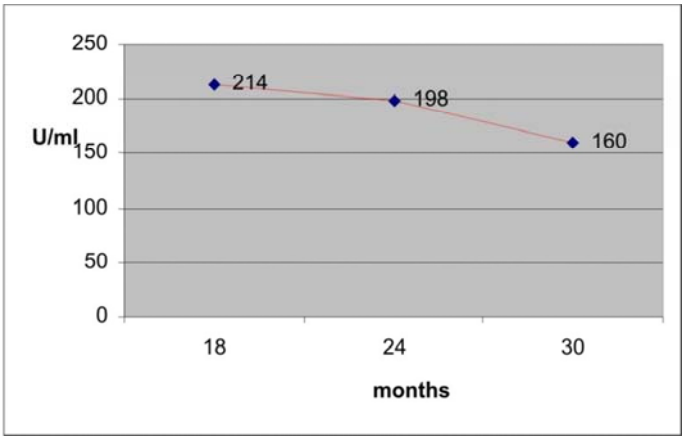

Figure 3. CA 19-9 at 18, 24 and 30 months.

In addition, for the next patient, who had cephalic T2N0M0 neoplasm who underwent through DPC-Whipple R0 in 11.08.2004, and was also still alive in October 2006, we could observe CA19-9 levels varying from 14598 U/mL at 17 months, 26246 U/mL at 18 months, 35602 U/mL at 19 months, and 79902 U/mL at 22 months (Figure 4).

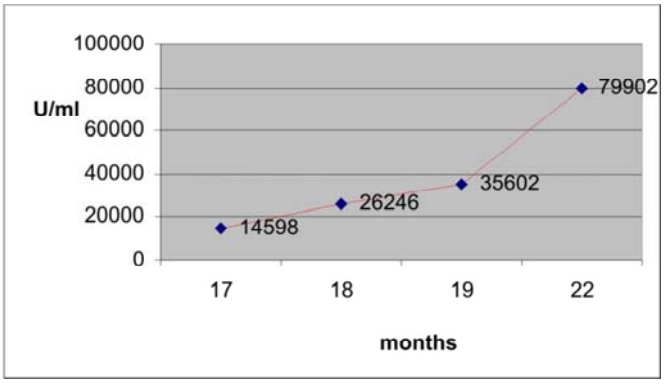

Figure 4. CA 19-9 at 17, 18, 19 and 22 months.

Moreover, for another patient with T2N1M0 and DPC-Whipple R0 in 20.10.2004, which was also was alive in October 2006, the noticed the following CA 19-9 levels: 5763 U/ml at 11 months, 7241 U/mL at 12 months, 3560 U/mL at 19 months, 18800 U/mL at 22 months (Figure 5) and the ACE of 20 at 14 months.

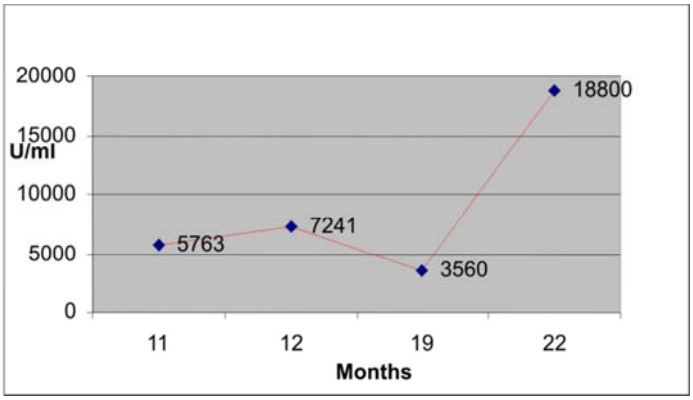

Figure 5. CA 19-9 at 11, 12, 19 and 22 months.

Still , for one patient with cephalic T3N1M0 R0 neoplasm, which also survived for 16 months, we could observe the following CA 19-9 levels: 525 U/mL at 8 months, 793 U/mL at 12 months, 1730 U/mL at 13 months and also 7816 U/mL at 14 months (Figure 6).

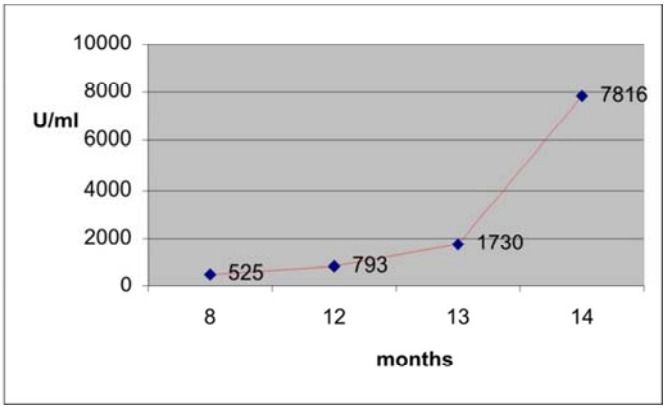

Figure 6. CA 19-9 at 8, 12, 13 and 14 months.

And finally we observed for one patient with TxNxM1 ABD, which survived for six months, that he had the CA 19-9 = 1273 U/mL at 1 month, 5305 U/mL at 2 months, 7162 U/mL at 3 months and 38586 U/mL at 4 months (Figure 7), and the ACE = 3 at 3 months.

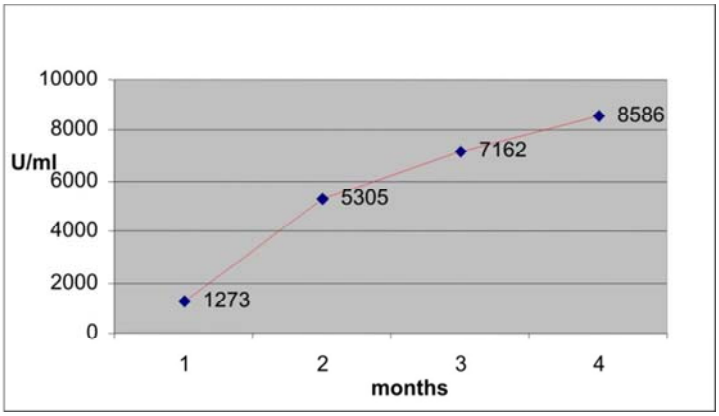

Figure 7. CA 19-9 at 1, 2, 3 and 4 months.

DISCUSSION

As previously mentioned, despite the numerous studies about pancreas cancer, little is known about the mechanistic of this disease. The resections for the cancer of pancreas have entered in the therapeutic arsenal for 65 years, but despite the fact that hundreds of articles were written on this subject, there is no unanimity of opinion concerning the efficacy of resection. In this way, a number of authors have reported a 5 years survival rate of 30% or even 58%, being supportive of resection (Kayahara et al., 1995).

Thus, the prognosis of the patients with pancreatic cancer and who have an indication for resection with curative intent is determined by lymphatic metastasis, invasion of the vascular walls, of the peripancreatic nerve plexuses and also by the micrometastases in the surrounding tissues and organs.

In fact, the factors which were found to have a significantly independent prognostic after applying the multivariate analysis were resection negative margins, tumoral diameter, estimated blood loss < 750 ml, good/moderate tumor differentiation, postoperative chemotherapy or location of the tumor in the head, neck, and uncinate process.

Also, lately there is an increased awareness regarding the relevance of some tumoral markers such as CA19-9 (carbohydrate antigen 19-9) and CEA (carcinoembryonic antigen) in this disorder (Perkins et al., 2003; Boehm et al., 2000).

In this way, CA 19-9, a bystander and response indicator to the adjuvant treatment in the oncology services, which was first described by Koprowski et al., represents a tumoral tissue associated carbohydrate antigen found on the surface of several types of gastrointestinal tumoral cells. Thus, Koprowski immunized colorectal carcinoma cell lines in mice and then isolated CA 19-9 monoclonal antibodies from the mice splenocytes.

Moreover, subsequent studies indicated that the antigen is normally present in salivary mucus and pancreatic exocrine secretion, which makes it, despite its origin in tumor colorectal cell lines, currently useful in the diagnosis, prognosis, evaluation and monitoring of patients with pancreas cancer (Berger et al., 2004).

Regarding the previous studies in this area of research, some authors have tried to prove the usefulness of sequential determination of the CA 19-9 dynamics in the serum of patients during postoperative monitoring period. In this way, probably the first study in this direction was carried out in 1986 at the National Cancer Institute Bethesda, the authors noticing that patients who

experienced a decrease in the serum levels to normal values after surgery had better survival than those to which the marker value maintained on the same increased level. They have also shown that an increase of the level of CA 19-9 over 95U/mL, or four times its lowest value, immediately postoperatively, is a prediction factor of the progression of the disease (Glenn et al., 2008).
Also, other authors have shown that elevated serum levels during the postoperatory period precede the occurrence of visible lesions by or by clinical examination within 2 to 9 months (Tian et al., 1992).
In addition, Berger et al. analyzed retrospectively 129 patients who had determined the CA 19-9 before curative resection, between 1990 and 2002. In this way, the authors studied not only the correlation between the antigen level and recurrence/survival, but also the prognosis of patients with undetectable antigen in the serum. The CA 10-9 preoperatory level was grouped into four categories: undetectable, normal < 37, increased 37-200, highly increased > 200 U/mL. The results ranged from 0 to 16.300 U/mL. Also, the overall median survival and 5 years survival were respectively 19 months and 11%.
In addition, survival was similar for the non-secretors and those with normal levels and both groups had statistically significant survival, larger than the other 2 groups with elevated over normal values (p= 0.003).
Also, the only significant predictive factor for survival, after univariate and multivariate analysis, was the presence of tumoral adenopathies (p = 0,015 and 0,002) and the level of CA 19-9 (p = 0.003 and p < 0.0001). Although the normal and undetectable values group of patients presented an advanced disease, the overall survival was still superior.
Moreover, there are few studies in the literature about CA 19-9 non-secretory patients. In this way, it may be foreseeable for these patients to have a worse prognosis because the level of antigen can not be assessed and, therefore, it is not possible to make the prediction of the treatment response or the recurrence and survival.
However, in this study the non-secretory group had the same prognosis as the normal antigen values in the preoperatory group. Also, the median survival of these two groups of patients was similar, respectively 32 and 35 months.
Furthermore, these patients had a significantly better survival rate than those with high levels of the antigen, as demonstrated by univariate and multivariate statistical analysis. In fact, the patients with undetectable levels had a much higher median recurrence-free survival value as compared to the other groups: 27 vs. 14, 10 and 10 months respectively, despite the fact that it had no statistical significance.

CONCLUSIONS

Our results are showing the relevance in determining these specific tumoral markers, especially as predictors for recurrences after pancreatic neoplasm surgery, since the determination of the serum level of CA 19-9 seem to be relevant in the cases when the antigen level drops immediately after the surgery, then increases progressively, highlighting the emergence of recurrence.

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