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Tumor markers in pancreatic cancer – literature review

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Abstract: Pancreatic cancer remains an important health problem worldwide, being associated with an overall poor prognosis. One of the most important reasons for these poor outcomes is the late diagnosis of the disease, when radical surgery is not longer feasible. In order to improve the prognosis, attention was focused in determining the most appropriate protocols of early diagnosis of this aggressive malignancy. For the moment the most common used marker remains CA 19-9 which seems to be appropriate for both diagnosis and follow-up but its sensibility and specificity remains still low.

Key Words: pancreatic cancer, CA 19-9, overall survival, surgery.

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Introduction

Although is situated on the 13th place among human malignancies, pancreatic cancer ranks as the 5th cause of cancer related death in Europe, being one of the most aggressive malignancies. This fact is partially related to the moment of diagnosis and presentation, only 20% of new diagnosed patients being considerate candidates for surgery and only half of them being resectable at the moment of surgery. However in cases in which surgery is feasible, the 5 year overall survival rate reaches 4-26% while in cases with unresectable disease the overall survival decreases up to 5-12 months (Duffy et al 2010).

The role of screening tests for diagnostic and follow up of patients with pancreatic cancer

Screening and early diagnosis of pancreatic cancer using tumor markers still represents an important health problem worldwide. For cases already diagnosed with chronic pancreatic diseases tumor markers can be efficiently used as screening tests. Once the histopathological diagnosis has been established, tumor markers are used for follow up of these patients (Ruckert et al 2010). The main subtypes of tumor markers are tumor associated antigens (carbohydrates, glycoproteins, mucines, cytokeratines), enzymes, oncofetal antigens, ectopic hormones and other peptides; however, the most frequently used are tumor associated antigens. Among carbohydrate types of antigens, the most frequently used are CA 19-9, CA 50, CA 125 and CA 242 (Ruckert et al 2010).

CA 19-9

Although it was initially seen in colo-rectal cancer, CA 19-9 has become the most common used tumor marker in pancreatic cancer; it seems that in adults CA 19-9 is found in up to 80% of normal pancreatic cells in adults. In order to distinguish between pancreatic cancer and chronic pancreatitis, CA 19-9 has thought to have a sensibility of 70-90% and a specificity of 68-91% (Ruckert et al 2010).

In 1990 Steinberg et al (Steinberg 1990) compared the results of 24 studies and demonstrated that for a cut-off of 37 kU/l the diagnostic sensibility was 81% while the specificity was 90%. However, the National Academy of Clinical Biochemistry recommends the utilization of CA 19-9 only in association with other investigations such as endoscopy or computed tomography in order to evaluate the necessity of performing more invasive maneuvers such as ERCP, fine needle aspiration or diagnostic laparoscopy. False positive reactions can be encountered in benign biliary obstruction while false negative tests can be seen in Lewis a-b genotype. For Caucasian persons, in whom this genotype is seen in 5-10% of cases, the maximum sensibility of CA 19-9 reaches up to 90-95%. Benign diseases associated with high values of CA 19-9 are chronic and acute pancreatitis, hepatic cirrhosis, cholangitis and obstructive jaundice while other malignant conditions associated with increased values of CA 19-9 are cholangiocarcinomas (67%), gastric cancer (41%), colo-rectal cancer (34%), esophageal cancer (22%) or hepatocellular carcinoma (49%). The sensibility of CA 19-9 is low in early stages or in cases with low dimension tumors; in cases with tumor dimensions fewer than 3 cm only half of the patients will report increased values of CA 19-9. Also in cases

with undifferentiated tumors the values of CA 19-9 are lower when compared with cases with moderate or well differentiated tumors.

In order to increase the accuracy of diagnosis of pancreatic cancer, some authors recommend the association between CA 19-9, CRP and bilirubin. A study conducted by LaGreca et al between 2005 and 2009 involved 102 patients with bilirubin levels higher than 2 mg/dl in whom CRP and CA 19-9 were determined. The study group was splited in two subgroups with benign, respectively malignant, diseases and sensibility, specificity and predictive values of CA 19-9 and were determined. Among cases with malignant lesions CA 19-9 encountered increased values in 82,3%, while CRP was increased in 49% of cases; when determining the same parameters in benign lesions, increased values of CRP were encountered in 66.6% of cases. The study concluded that increased values of CA 19-9 and bilirubin were seen in malignant lesions while CRP was rather increased in benign conditions. A cut-off of 32 U/mL for CA 19-9 was associated with a sensibility of 82.3%, specificity of 45% and a positive predictive value of 59.1%. At a cut-off of 100 U/ml the same parameters were 68.6%, 64.7% respectively 66%. CA 19-9/bilirubin ratio had a sensibility, specificity and a predictive value respectively of 49%, 78.4% and 69.4% while the CA 19-9/CRP ratio had a sensibility, specificity and a predictive value respectively of 76.5%, 68.6% and 70.9%. In conclusion, the influence of inflammation on CA 19-9 values can be reduced when using the last ratio (La Greca et al 2012). Differentiation between benign and malignant diseases of pancreas can be also performed by studying CA 19-9 modifications after endoscopic biliary drainage. Marelli et al conducted a study on 128 patients: 87 of them were diagnosed with pancreatic cancer (86% of them reporting CA 19-9 concentrations higher than 37 U/ml) while 41 had benign pancreatic disorders (61% of them reporting CA 19-9 concentrations higher than 37 U/ml). After performing a biliary drainage, CA 19-9 values decreased in half of the cases with malignant disorders and in all cases with benign conditions. The same study concluded that CA 19-9 values higher than 90 U/ml after biliary drainage indicates the presence of a malignant lesion (Marrelli et al 2009). Another way to appreciate the benign versus malignat character of a pancreatic lesion in cases presenting pancreatic cysts is by studying the liquid obtained by cyst punction. High values of CA 19-9 and CEA in cyst liquid orientates the clinician to a malignant lesion (Snozek et al 2009).

CA 19-9 also represents an important prognostic factor in patients with pancreatic cancer in both resectable and unresectable diseases. In patients in whom high preoperative values are encountered an early recurrence can be expected even after complete surgical resection (Ruckert et al 2010). In cases with resectable lesions both pre-operative and post-operative CA 19-9 values are correlated with the overall survival.

The study conducted by Ferrone et al (Ferrone et al 2006) concluded that a cut-off value of 1000kU/l for CA 19-9 can provide an efficient stratification between patients with good respectively poor prognosis if normal levels of bilirubin are present. The same study established that the most appropriate postoperative cut-off value of CA 19-9 is 200 kU/l.

A study conducted by Shun Zhang et al estimated the role of CA 19-9 in predicting the tumor resecability. A lot of 104 patients was analysed; in 58 cases (55.77%) the lesion was resecable while in the other 46 cases (44.23%) an unresectable tumor was found. For a cut-off value of 353,15 U/ml the sensibility and specificity of CA 19-9 in predicting the tumor resecability was 93.1% respectively 78.3% while the positive respectively negative predicting values were 84.38% and 90%. These data present particular interest due to the fact that almost in half of the patients diagnosed with imagistic resectable tumors, the lesions prove to be in fact unresectable at the moment of surgery (Zhang et al 2008).

However, it seems that CA 19-9 is also useful in order to monitorise the response to chemotherapy in patients with unresectable pancreatic cancer. A study conducted by Maisey et al involved 154 patients with unresectable pancreatic cancer who were submitted to systemic chemotherapy. CA 19-9 was determined before initiaiting chemotherapy and after 6 weeks of oncologic treatment, using an enzimatic immunologic method (Axsym-Abbott Diagnostics Laboratory). The upper normality limit was established at 37 U/ml. Due to the posibility of interference of bilirubin levels, the authors excluded from their study the cases with bilirubine levels higher than 30 µmol/l. The median value of CA 19-9 at the beginning of the treatment was 958 U/ml, while after ending the treatment the median value was 998 U/ml. In patients with a reported value higher than the median value the overall survival was significantly lower than for those with lower than median values: 165 days versus 337 days (p=0.0004). this also proved to be a significant prognostic factor in multivariate analysis too. Another important prognostic factor proved to be the presence of a decreasing of more than 20% for CA 19-9 (Maisey et al 2005).

Dong et al studied the role of CA 19-9 in cases with resectable pancreatic tumors on a lot of 120 cases; the authors measured CA 19-9 values two weeks before surgery by electro-chemoiluminiscence using a Roche Cobas E601 analisor. For a cut-off value of 338.45 U/ml the sensibility, specificity and accuracy of Ca 19-9 in order to predict the overall survival were 60%, 66.7% respectively 64.2% while the 1 year overall survival was 62.5%. At this cut-off value CA 19-9 proved to be an independent prognostic factor of poor prognosis. When evaluating the influence of CA 19-9 on TNM stages, the same study failed to demonstrate a significant differention between T1/T2 and T3/T4 stages (Dong et al 2014).

A special category of patients was the one with preoperative undetectable values of CA 19-9. In a study conducted on 129 patients with pancreatic tumors the patients were classified according to 4 categories: the first one included patients with undetectable values of CA 19-9, the second category included cases with CA 19-9< 37 u/ml (established as normal values), the third category included patients with CA 19-9 ranging between 38- 200 U/ml, while the last category included cases with CA 19-9>200U/ml; the highest encountered value was 16300 U/ml. TNM stadialisation was also evaluated. The authors concluded that even if pre-operatively CA 19-9 encountered undetectable values, an aggressive surgical approach should be taken in consideration (Berger et al 2004).

The role of Ca 19-9 during the postoperative follow-up

Even if complete resection is performed, pancreatic cancer has a high risk of developing local or distant recurrence. However, it seems that CA 19-9 is an appropriate method in order to detect the tumor relapse. Although it has been shown that a biochemical

recurrence manifested through increasing values of CA 19-9 might appear with a few months earlier before the clinic or imagistic detection of the recurrence, the moment of re-introducing systemic therapy remains to be discussed (Ruckert et al 2010). More than that, ASCO (American Society of Clinical Oncology) guidelines consider that a positive diagnosis of recurrence should be done only if clinical, imagistic and biological modifications are all present (Duffy et al 2010).

However, once a positive diagnosis of recurrence has been established, CA 19-9 is also useful in order to monitorise the response to systemic chemotherapy. It seems that diminishing values of CA 19-9 with more than 25% report an improved prognosis when compared to patients with constant values. However, for seriate determination, the same method of analysis and measurement should be performed (Duffy et al 2010).

A study conducted by Hess et al in 2008 demonstrated that a decrease of more than 50% of CA 19-9 values in the 42nd day after 2 cycles of chemotherapy is associated with an improved prognosis. The same study established a strong correlation between pretreatment values of CA 19-9 and overall survival (Hess et al 2008). Another study conducted in 1998 by Gogas et al involved 39 patients with unresectable pancreatic cancer who were submitted to palliative chemotherapy; in all cases initial values of CA 19-9 were determined, then the marker's value were monitored after each cycle of chemotherapy. A significant decrease was considered whether the tumor markers diminished with more than 15% at two serial measurements performed at an interval of 3 weeks. Decreased values were seen in 13 cases, constant values were registered in 7 cases while increased values were seen in 16 cases; the median overall reported survival for the three groups were 333, 253 and 158 days respectively. Monitoring CA 19-9 was associated with a sensibility and specificity rate of 67% respectively 69%; the authors concluded that CA 19-9 should be used in association with other paraclinical studies in order to increase the capacity of response prediction (Gogas et al 1998).

CA 50

CA 50 is another tumor marker with comparable sensibility and specificity with CA 19-9. However association with jaundice and cholestasis syndrome decrease CA 50's diagnosis specificity (Duffy et al 2010, Ruckert et al 2010).

CA 242

CA 242 has a similar structure with CA 19-9 and CA 50, being associated especially with colo-rectal and pancreatic cancer. In pancreatic cancer the reported sensibility and specificity reach 57-82% respectively 76-93%. Association with jaundice can provide false positive reactions; due to this reason CA 242 is not very often used in this pathology (Duffy et al 2010, Ruckert et al 2010).

CA 195

CA 195 has a lower sensibility and specificity when compared to CA 19-9.

CA 125

CA 125 encounters a low utilization in pancreatic cancer due to the low sensibility and specificity, high values being also present in hepatic cirrhosis (up to 64% of cases), acute or chronic hepatitis (up to 23% of cases), acute or chronic pancreatitis (35% of cases)

or in jaundice (in almost 35% of cases) (Ruckert et al 2010). A study conducted by Haglund in 1986 showed that the association between CA 19-9 and CA 125 can increase the diagnostic specificity of CA 19-9 with only 6% (Haglund 1986).

CEA

CEA is a glycoprotein present in the fetal liver, pancreas and gastro-intestinal tract; in adolescents it can be seen in low quantities in colon and endometrial tissues. The sensibility and specificity of this marker in pancreatic cancer widely vary between 25-54% respectively 75-91%, so it cannot be introduced as part of the standard protocol of diagnosis or follow up in pancreatic cancer (Ruckert et al 2010). However, it seems that CEA can be used in monitoring the treatment response in patients with Lewis a-b genotype (Duffy et al 2010).

A study conducted on 324 patients submitted to radical pancreatic resection estimated the role of CA 19-9 respectively CEA monitoring during the peri-operative period. Obtained values of the two markers were introduced in a formula in order to determinate an index (index= CEA×CA19-9) which seemed to have a strong correlation with overall prognostic. Results of the study have shown that an index value higher than 500 represents an independent prognostic factor associated with poor prognosis (p=0,021). This conclusion might have a strong impact on deciding which is the most appropriate therapeutic option (Kanda et al 2014).

POA

POA represent a group of polyclonal antibodies against fetal pancreas used in oncogenes detection in patients with pancreatic cancer. The sensibility of this test is variable, while the specificity is decreased in cases with other associated hepato-biliary diseases.

Other proposed tumor markers in diagnosis and follow up of patients with pancreatic cancer are TPA and TPS cytokeratines, DuPAN 2, Span-1 and CAM17.1 mucines, enzymatic markers such as TATI, Tu M2-PK, Elastazis-1, Galactoziltransferasys II izoenzyme, oncofetal antigenes such as AFP and other unspecified markers such as EPM-1, OPN, CEACAM1 or MIC1. However these markers have not been included as standard tests, further evaluation still being necessary.

Conclusions

Although the sensibility and specificity of CA 19-9 are not very high, this tumor marker still has the higher clinic applicability. In time further studies of molecular biology are expected in order to determine some other molecular markers with higher specificity.

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