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Predictive and Prognostic Value of Human Equilibrative Nucleoside Transporter 1 in Advanced Pancreatic Carcinoma

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Abstract

Background: Pancreatic cancer is a very aggressive disease. 5-year survival rates remain low at 10% to 30% even with adjuvant therapy, as most patients will succumb to the disease secondary to high rate of local and systemic recurrences. Gemcitabine is one of the drugs of choice for the adjuvant treatment for patients with pancreatic cancer. The drug is transported into pancreatic cancer cells primarily by human equilibrative nucleoside transporter 1 (hENT1).

Aim of Study: To evaluate hNET-1 protein expression in patients with advanced pancreatic cancer treated with gemcitabine-based chemotherapy as a predictive factor for the response of treatment as well as prognostic marker for overall survival and disease progression.

Patients and Methods: Prospective and retrospective study was conducted on 30 patients presented with advanced pancreatic cancer; Immuno-histochemical staining of tumor tissue was performed for detecting hENT 1 expression. All the patients have been treated with gemcitabine based chemotherapy.

Results: Sixty percent of patients had high hENT 1 expression and 40% had low hENT1 expression. Overall survival after median follow-up of 14 months showed that patients with high hENT1 expression had longer Overall survival than patients with low hENT1 expression and the difference was statistically significant (p=0.0025) respectively. Further, patients with high hENT1 expression showed longer disease free survival than patients with low hENT1 expression, and the difference was statistically significant (p=0.002).

Conclusion: A high level of hENT 1 expression is significantly associated with a longer survival in patients who received gemcitabine mono therapy. Hence, the study suggests hENT 1 expression as potential assay for the prediction of response to gemcitabine based chemotherapy.

Key Words: *Pancreatic cancer – hENT1 – Gemcitabine– Survival – Marker.*

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Introduction

PANCREATIC cancer representing the fourth leading cause of cancer-related mortality. In Egypt the annual mortality rate from pancreatic cancer has increased by 147.7% since 1990, with an average of 6.4% a year. In 2013 males mortality rate was 2.4% per 100,000 cases while it was 1.7% in females.

Pancreatic cancer (pancreatic ductal adenocarcinoma) constitutes ninety percent of all primary malignant tumors discovered from the pancreatic gland. In up to 60-70% the tumor is situated in the head and the remaining is founded in the body and in the tail.

Due to aggressiveness of the tumor, the diagnosis of Pancreatic cancer is rarely made at an early stage. More than 90% of Pancreatic cancer appears in the late stage of disease and only 10% of patients have resectable tumors at the time of diagnosis **[1]**.

Many risk factors may be suggested in the development of pancreatic carcinoma such as age, smoking, diet, obesity, family history, chronic pancreatitis and alcohol consumption **[2,3]**.

Many prognostic factors have been investigated thoroughly, especially from the histologic examination of the resected cancer tissues. For example, lymph node metastasis, the status of resection margins, tumor grade, tumor size, lympho-vascular invasion, and perineural invasion are important in pancreatic cancer as a prognostic factor **[4,5]**.

The symptoms of pancreatic adenocarcinoma do not usually appear in early stages of the disease, and are individually not characteristic for the

disease. The symptoms at diagnosis vary according to the location of the tumor in the pancreas, which divided into the head, the neck, and the body, ending in the tail [6].

Regardless of a tumor's location, the most common symptom is unexplained weight loss, which may be considerable. People diagnosed with pancreatic cancer will have had nausea, vomiting and fatigue. Tumors in the head of the pancreas typically also cause jaundice, pain, loss of appetite, dark urine, and light-colored stools. Tumors in the body and tail typically also cause abdominal pain [6].

The treatment of pancreatic cancer is undertaken with two different ways. The first is radical surgery for patients with early stage of cancer, mainly stage I and some of stage II. In all other cases, the aim of treatment is the palliation of the several distressing symptoms related to this cancer [7].

Gemcitabine is the standard chemotherapy treatment for pancreatic cancer [8], but its efficacy is limited; only 15% of patients with advanced pancreatic cancer and up to 30% in general [9] can be expected to respond to treatment.

Gemcitabine strongly hydrophilic, passive diffusion through the hydrophobic cellular plasma membrane lipid bilayer is slow. In order to increase the diffusion through cellular membrane, gemcitabine requires physiologic nucleoside transporter proteins to cross the plasma membrane [10]. Because gemcitabine is a prodrug, it has to be phosphorylated after entering the pancreatic cancer cells in order to have a cytotoxic effect. This rate-limiting step is carried out by the enzyme deoxycytidine kinase (dCK) [11].

hENT1 proteins are trans-membrane glycoproteins that located in the plasma membrane. They are capable of transporting gemcitabine in the direction of the concentration gradient, which lead for incresing gemcitabine effects on the pancreatic cancer cells [12]. Further, many studies, have shown that gemcitabine enter pancreatic cancer cell primary by hENT1 transporters, and the cells lacking hENT1 are highly resistant to gemcitabine, confirming the importance of hENT1 for the activity of gemcitabine [10,13].

Recent research has showed that differences in the expression of genes, including hENT1 and enzymes involved with gemcitabine metabolism such as dCK may be predictors of the efficacy of gemcitabine treatment for pancreatic cancer. Several studies have indicated that high expression of hENT1 is associated with longer overall survival (OS) and longer disease-free survival (DFS) [14].

Patients and Methods

The Retrospective study carried out at clinical oncology and nuclear medicine department Tanta university hospitals from July 2012 to July 2016. Thirty patients with locally advanced or metastatic pancreatic carcinoma who received or planned to receive Gemcitabine based regimen was enrolled.

Inclusion criteria:

- Age of patients <70 years.
- Performance scale 0-2.
- Adequate CBC, Liver and kidney function tests.

Exclusion criteria:

- Prior chemotherapy or radiotherapy treatment.
- Pregnant, lactating mothers or active infection.
- Previous history of hypersensitivity reactions.
- Uncontrolled medical illness or other malignant disease.

The medical files of all patients included in this study were gathered. Scientific data were properly collected, revised and analysed to evaluate survival rate and loco-regional treatment failure and metastases. Privacy of all patients' data was guaranteed and there were code number for every patient's file that includes all investigations.

The following data were collected from medical reports for proper diagnosis and staging:

A - History and clinical examination:

1- *History:*

- Personal history including (name, age, job, residency, marital status, number of children, socio-economic status, smoking index and performance).
- Present history including symptoms and its duration.
- Past history including medical co-morbidities and previous treatment.
- Family history including cancer history.

2- *Reported clinical examination including:*

- General examination for detection of symptoms and signs suggestive of distant metastases, any associated disease.
- Assessment of the performance status of the patient according to ECOG.
- Local examination of the abdomen including Inspection and palpation of entire abdomen and pelvis.

B- Work up:

1- *Routine laboratory investigations:*

- Complete blood picture with total and differential count.
- Liver function tests "bilirubin, liver enzymes and serum albumin.
- Renal function tests "blood urea and serum creatinine.
- Fasting and postprandial blood sugar was done for all patients at initial presentation and before the start of every cycle of chemotherapy.
- Tumour markers e.g.: CA 19.9, CEA.

2- *Radiological imaging:*

- Chest X- rays.
- CT or MRI abdomen-pelvis.
- Bone scans if needed.
- PET - CT if indicated.

Tissue biopsy:

All tissue biopsies were taken by u/s guided biopsy, CT guided biopsy or by excision biopsy. All specimens were formalin fixed and paraffin embedded.

Chemotherapy:

Patients received regimens of Gemicitabine chemotherapy (day 1,8,15 by 1000mg/m^2 IV over 30 minutes) repeat cycle every 28 days. Patients were followed-up weekly during chemotherapy for symptoms and signs of toxicity either haematological toxicity (anaemia, leucopenia and thrombocytopenia) or non-haematological (vomiting, diarreha and mucositis) according to WHO cancer toxicity criteria **[15]**.

All patients were assessed at end of treatment and every 3 months for at least 6 months as follow **[15]**.

- *Complete response (CR):* Is defined as the disappearance of all signs of disease both at clinical and radiological examination.
- *Partial response (PR):* Is defined as reduction of more than 50% in the sum of products of the largest perpendicular diameter of all tumour localizations, with absence of new tumour lesions.
- *Stable disease (SD):* Is defined as reduction of less than 50% or an increase less than 25% of tumour lesions.
- *Tumour progression (DP):* Is defined as increase more than 25% in the size of tumour Lesions or the appearance of a new lesion.

Patients follow-up:

Liver function test, creatinine and electrolyte every cycle and as clinically indicated.

Imaging of the chest, abdomen and pelvis every 3-6 months based on risk of recurrence and then as clinically indicated.

Tissue Preparation and Immunostaining:

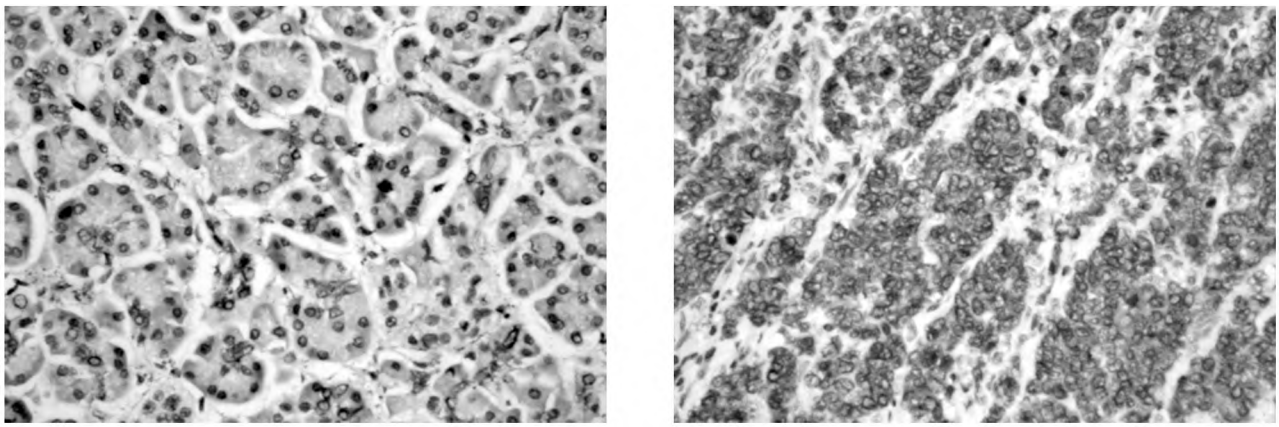
Representative tumour paraffin blocks were sectioned at 3μm thickness for IHC studies. The sections were deparaffinised with three immersions in xylene baths (10 minutes each) followed by serial washes in graded alcohol from 100 to 70%. After rinsing in water, slides were placed in 250 mL of high pH 1X DAKO target antigen retrieval solution and microwaved 10 minutes at 100ºC. After cooling in water for 6 minutes, slides were rinsed with water and peroxidise blocked in 3% hydrogen peroxide solution with methanol for 10 minutes then washed in running water for 10 minutes. PBS (pH 7.2) was used for rinsing before incubation in a humidified chamber overnight at 4ºC with appropriate dilutions of anti-hENT 1 mouse monoclonal antibody. Then, sections were rinsed with PBS, immersed in buffer for 5 minutes, incubated with goat anti-mouse dextran conjugate (DAKO Envision) for 30 minutes, followed by soaking in PBS. DAKO diaminobenzidine liquid chromagen was placed on the samples for 5 minutes, then rinsed, after which the slides were soaked in 1% CuSO4 for 5 minutes. Subsequently, the sections were rinsed, counterstained with hematoxylin, dehydrated through graded alcohol and xylene, and finally cover slipped. Omitting the primary antibody provided negative controls. The pathologist, who was blinded to clinical characteristics and outcomes, has assessed immunostaining.

Immunohistochemical evaluation:

Staining of hENT1 protein was assigned a score from 0 to 3 based on staining intensity with 0=no staining, 1=weakly positive, 2=moderately positive, and 3=strongly positive. The percentage of adenocarcinoma cells staining at each intensity level was recorded for each specimen. A final score was determined by multiplying the intensity score and the percentage of the specimen. For example, if a specimen exhibited a staining distribution of 30% 1+ and 60% 2+, the final score is 150 (1X30+ 2X60). Therefore, the weighted scores ranged between 0 and 300 **[8]**.

The staining intensity for the hENT 1 protein and the percentage of positive tumor cells was scored, and a composite score (hENT1 score) was obtained by calculating the sum of these two scores.

The staining intensity for the hENT 1 protein was assigned a score from 0 to 3 based on staining with 0+ thus indicating no staining; 1+, weakly positive; 2+, moderately positive; and 3+, strongly positive. The percentage of positive tumor cells was scored as follows: 0+, no positive tumor cells; 1+, <50% positive cells; 2+, 50-80% positive cells; and 3+, ›_81% positive cells. According to the hENT1 score, we classified tumors with the tumors with scores of 0-3 as having a low hENT 1 expression and tumors with scores of 4-6 as having a high hENT 1 expression [16] Example Fig. (1).



(A) (B)

Fig. (1): Representation example for the immunohistochemical (A) Weak hENt1 expression and (B) Strong hENT1 expression).

Results

This is a Retrospective study included 30 patients with advanced pancreatic carcinoma (12 patients prospectively and 18 patients retrospectively) presented at clinical oncology and nuclear medicine department, faculty of medicine, Tanta University, Tanta, Egypt during the period from July 2012 to July 2016.

According to patients' characteristics (age, gender, smoking habit, diabetic mellitus, performance and clinical response) (patient's characteristics are shown in Table 1). The majority of patients were male patients (17/30, 56.6%), older than 50 years (17/30, 56.6%), smoking history positive (16/30, 53.3%), Diabetic (16/30, 53.3%). Patients with Performance status 1 represented the majority of cases (16/ 30, 53.3%), while PS was zero in nine patients (9/30, 30%), and five patients were 2 (5/30, 16.7%).

Regarding to tumor size, most of patients presented with T3 tumor (12/30, 40%) with stage III-IV (16/30, 53.3) and the majority of tumors were found in head of pancreas in (19/30, 63.3%), poorly differentiated (13/30,43%) also, most of the patients represented with LN metastasis (20/30, 67%).

Clinic -pathological factors and hENT1 expression:

In high hENT1 group most of patients were <50 years (10/30, 33.3%), males (13/30,43.3%), smokers (16/30,53.3%), suffering from diabetes (13/30, 44%), presented with head tumors (16/30, 46.6%), tumor size T2 (9/30, 30%), LN positive (15/30, 50%) and moderate differentiated tumor (23.3%) presented with stage I-II (9/30, 30%). But all of them were not significantly positively correlated with hENT1 expression (Table 2).

About patients with low hENT 1 group, most of patients were older than 50 years (7/30, 23.3%), females (8/30, 26.6%) with negative smoking history (12/30, 40%) and not diabetic (30%). The majority of tumors were located in body of pancreas (6/30, 20%), T3 (20%), no LN metastasis (20%), and with poorly differentiated pathology (23.3%), stage III-IV (10/30, 33.3%). But also after analysis of data all of those factors were not significantly positively correlated with hENT1 expression.

According to response to treatment and the effect of hENT 1 expression on it, in high hENT 1 expression group the majority of patients showed PR (8/30, 27%), SD in (3/30, 10%) where only four patients showed PD (4/30, 14%). While in low hENT 1 group the majority of patients showed PR (5/30, 16%) whereas PD in (3/30, 10%) and no patients showed SD (0%). Reflecting a significant correlation between hENT 1 expression and response rate to treatment with gemcitabine based chemotherapy (p=0.0331).

Concerning performance status, in high hENT 1 group most of patients were performance status 1 (9/30, 30%) as well as in low hENT 1 group the

majority of patient were 1 (23.3%) but did not reflect any significant correlation between performance status and hENT1 expression (p=0.147).

hENT1 expression and overall survival:

Data plotted in Fig. (1) show a survival plot, which found that the median over all survival was 4 months (95% CI, 2.868–5.132) for patients with low hENT1 expression and 9.5 months (95% CI, 8.70210.298) for patients with high hENT 1 expression (HR for death 0.470; 95% CI, 8.079–9.921; p=0.001) which point to a significant positive correlation between hENT1 expression and over all survival Fig. (2).

hENT1 expression and progression free survival (PFS) relation:

Results presented in Fig. (2) show a survival plot which revealed that the median PFS was 2 months (95% CI, 1.467–2.533) for patients with low hENT1 expression and 3.5 months (95% CI, 3.010–3.990) for patients with high hENT 1 expression (HR for disease recurrence, 0.235; 95% CI, 2.540–3.460; p=0.002). Indicating a significant positive correlation between hENT1 expression and progression free survival for the tested patients. Fig. (3).

Table (1): Patient's and tumor characteristics.

Factor	Total no. of patients n=30
Age (years):	
<50	13 (43.3%)
>50	17 (56.7%)
Gender:	
Male	17 (66%)
Female	13 (34%)
Performance:	
0	9 (30%)
1	16 (53.3%)
2	5 (16.7%)
Smoking:	
Positive	16 (53.3%)
Negative	14 (46.7%)
DM:	
Positive	16 (53.3%)
Negative	14 (46.7%)
Tumor location:	
Head	19 (63.3%)
Body	8 (26.6%)
Tail	3 (10%)
LN:	
Present	20 (66.6%)
Absent	10 (33.3%)
Tumor size:	
T2	10 (33.3%)
T3	12 (40%)
T4	8 (26.6%)
Grade:	
Well	7 (23.3%)
Moderate	10 (33.3%)
Poor	13 (43.3%)
Stage:	
I-II	14 (46.6%)
III-IV	16 (53.3%)

Table (2): Comparison of clinico-pathological factors based on hENT1 score for all patients (n=30).

Factor	No. of patients (%)		p-value
	High hENT 1 n=18 (60%)	Low hENT 1 n=12 (40%)	
Age (years):			
<50	10 (33.3%)	5 (16%)	0.271
>50	8 (26.6%)	7 (23.3%)	
Gender:			
Male	13 (43.3%)	4 (13.3%)	0.147
Female	5 (16.6%)	8 (26.6%)	
Tumor location:			
Head	14 (46.6%)	5 (16.6%)	0.289
Body	2 (6.6%)	6 (20%)	
Tail	2 (6.6%)	1 (3.3%)	
LN:			
Present	15 (50%)	5 (16%)	0.312
Absent	4 (14%)	6 (20%)	
Tumor factor:			
T2	9 (30%)	1 (3.3%)	0.0805
T3	6 (20%)	6 (20%)	
T4	3 (10%)	5 (16.6%)	
Grade:			
Well	5 (16.6%)	2 (6.6%)	0.1039
Moderate	7 (23.3%)	3 (10%)	
Poorly	6 (20%)	7 (23.3%)	
Performance:			
0	5 (16.6%)	4 (13.3%)	0.147
1	9 (30%)	7 (23.3%)	
2	4 (13.3%)	1 (3.3%)	
Smoking:			
Positive	16 (53.3%)	0 (0%)	0.109
Negative	2 (6.6%)	12 (40%)	
DM:			
Positive	13 (44%)	3 (10%)	0.218
Negative	5 (16.6%)	9 (30%)	
Clinical response:			
PR	8 (27%)	5 (16%)	0.0331
PD	4 (14%)	3 (10%)	
SD	3 (10%)	0 (0%)	
Stage:			
I-II	9 (30%)	5 (16.6%)	0.118
III-IV	6 (23.3%)	10 (33.3%)	

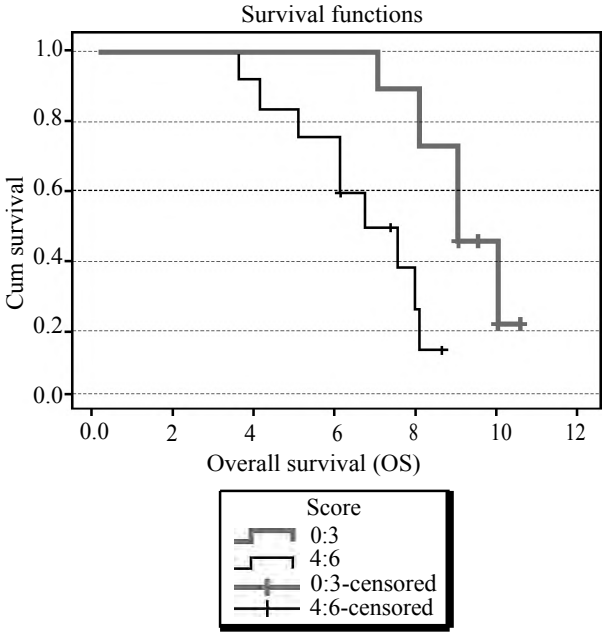


Fig. (2): hENT 1 score and progression free survival of high and low hENT1 patients.

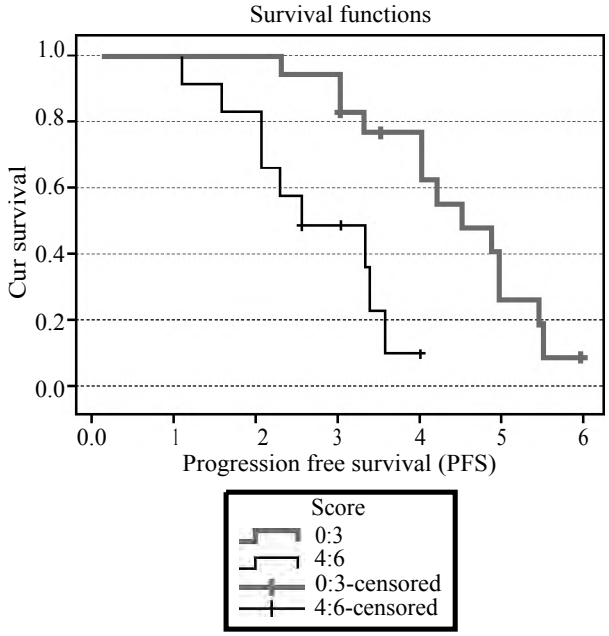


Fig. (3): hENT1 score and progression free survival of high and low hENT1 patients.

Discussion

The present study enrolled 30 patients with advanced pancreatic carcinoma, treated with adjuvant gemcitabine chemotherapy. Evaluation of hENT1 expression has been performed to assess its predictive value in correlation with treatment response and its prognostic value for overall survival and progression free survival.

The median age of patients enrolled in the present study was 50 years, patients with age <50 years represented (13/30,43.3%) while patients >50 years were (17/30,56.7%). This median age was not in the line with that reported by Morinaga et al., (2012) who reported a median age 64 years. On the other hand, Marchal et al., (2009) reported 58 years as a median age **[8,16]**.

Our study showed male patients predominance; male's patients were 17 (17/30,66%) while female's patients were 13 (13/30,34%) with male to female ratio (1.3:1). That is agreed with reported male predominance found by Morinaga et al., (2012) who reported 17 males and 10 females. They attributed that to the limited number of patients enrolled in their study **[16]**.

Smoking history was positive in nearly half of the patients in this study (16/30, 53.3%) while (14/30, 46.7%) were non-smokers. Our results matched with that reported by Giovannetti et al., (2006) and Yamada et al., (2016) **[17,18]**.

Marechal et al., (2009), Greenhalf et al., (2014) and Farrell et al., (2009) were interested in testing the effect of hENT1 on line of chemotherapy used for treatment of pancreatic cancer, they used 5-FU in a comparative group with gemcitabine chemotherapy **[8, 14,19]**.

The results did not demonstrate any significant association between OS or DFS and hENT1 expression in this treatment arm of 5-FU. hENT1 is an ancillary membrane transporter for 5-FU, primarily for reuptake of 5-FU into the cell. The primary membrane transporter of 5-FU at the apical membrane is the solute carrier family 22 member 7 protein (SLC22A7) suggesting that the contribution of hENT1 to 5-FU uptake into the cell has a negligible clinical effect **[20]**.

As well as several studies suggested hENT 1 evaluation has the strongest clinical support and a significant role as a predictive and prognostic marker with gemcitabine based chemotherapy **[11,14,16,18,19]**.

Assessment of hENT1 expression in the present study revealed that 18 patients were high hENT 1 while 12 patients were low hENT 1. Our findings matched with the results reported by several reports which surveyed hENT1 expression in patients treated with gemcitabine based chemotherapy and showed longer DFS and OS in patients with high hENT1 expression than patients with low hENt1 expression **[8,11,21]**.

On the other hand, different results were reported for study conducted on 21 patients where they found that 9 patients showed high hENT 1 expression and 12 patients showed low hENT1 expression. They suggested that the results obtained maybe caused by a bias due to limited patients enrolled in the study **[20]**.

The relation between patients' characters and hENT1 expression was investigated in previous studies **[16]**. In the present study we conducted a statistical analysis in order to evaluate the effect of some patient's characters on hENT1 expression for all the enrolled patients. Our results could not find any evidences suggesting any significant variations in hENT 1 expressions between all tested characters. Our results agrees with previous reports stated that hENT1 expression is not significantly influenced by patients characters and seems to be not dependent on age, gender, performance or smoking habit **[8]**.

In the present study, all enrolled patients have received gemcitabine as a mono therapy. Results showed that the response for treatment was varied. Hence, the median overall survival of all 30 patients was 9.5 months and the lowest recorded overall survival was 4 months.

The outcomes of the patients enrolled in our study was generally similar with that reported in other studies. For example, Vincent et al., (2011) reported that the median survival was 9 months for a trial enrolling 50 patients. They also reported the lowest survival was 3 months **[23]**.

In the present study, our results showed a strong significant positive correlation between hENT1 protein expressions and the overall survival and disease free survival.

Moreover, patients with a high level of tumour hENT 1 had a longer disease free survival and overall survival when compared with patients with low tumour expression of hENT1. Further, hENT1 expression in the tumour was indicated to be a significant and independent prognostic factor for overall survival by univariate analysis.

Our results are in line with the results of previous studies sassing the prognostic and/or predictive value of hENT1 in pancreatic cancer **[8,16-17]**. Retrospective studies on patients with various stages of pancreatic cancer treated with gemcitabine showed pancreatic cancer with higher expression of hENT 1 to have improved clinical outcomes after gemcitabine chemotherapy **[17,20]**. They attributed the improved overall survival and disease free survival in patients with high hENT1 expression to the more efficient gemcitabine uptake in the tumour cells.

Conclusion and Recommendations:

- A high level of hENT1 expression in pancreatic cancer found after Immune-histochemical analysis is significantly associated with a longer survival in patients who received gemcitabine mono therapy.
- hENT1 expression seems to be not dependent on patient variations such as gender, age and smoking which. Hence, its usability will not be affected by such variations and could be successfully used on a broad spectrum of patient.
- There is a need for a large randomised study including a large number of patients, genetics study hENT 1 and longer follow-up duration to apprehend the role hENT1 in neo-adjuvant or adjuvant chemotherapy or chemo-radiotherapy in tailoring the treatment of pancreatic cancer, assessing treatment response, disease free and overall survival.

Conflicts of interest:

The authors declare no conflicts of interest.

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القيمة التنبؤية والتقديرية للناقل البشرى النيكلوزى المكافئ لسرطان البنكرياس المتقدم

يعتبر سرطان البنكرياس واحد من أكثر الأمراض السرطانية التى تصيب الجهاز الهضمى أنتشاراً ويعد السبب الرابع بين أسباب الوفيات الناجمة عن الأمراض السرطانية. يتمثل حدوث سرطان البنكرياس لعلاقة خطية بعد سن الخمسين وزروة حدوث المرض بين العقدين السادس والسابع ونسبة حدوثه فى الذكور الى الإناث ١:٢.

الورم السرطانى الغدى أكثر أنواع سرطان البنكرياس أنتشاراً وأكثر أجزاء البنكرياس إصابة بهذا المرض هو رأس البنكرياس غير معروف حتى الأن و لكن التدخين والأفراط فى تناول الكحو ليات والدهون واللحوم فى الوجبات اليومية والألتهابات المزمنة التى تصيب البنكرياس ومرض البول السكرى وبعض العوامل الجينية سجلت كأكثر العوامل المصاحبة والتى تزيد من خطر سرطان البنكرياس.

الهدف من هذه الرسالة قياس تقييم القيمة التنبؤية والتقديرية للناقل البشرى النيكلوزى المكافئ لسرطان البنكرياس المتقدم فى المرضى الذين خضعوا للعلاج الكيميائى جمسيتابين.

أجريت هذه الدراسة في قسم الأورام والطب النووى بمستشفيات جامعة طنطا خلال الفترة من يوليو ٢٠١٢ ألى يوليو ٢٠١٦، وأرسلت العينات ليتم فحصها خلوياً بقسم الباثولوجى، وكلية الطب جامعة طنطا. تضمنت الرسالة ٣٠ مريضاً من مرضى سرطان البنكرياس المتقدم.

تم فحص ملفات المرضى لأخذ التاريخ المرضى والكشف الطبى والفحوصات من أشعة وتحاليل معملية والتحليل الباثولوجى لعينة الدم.

تم علاج المرضى عن تلقى العلاج الكيميائى جمسيتابين بقسم الأورام والطب النووى جامعة طنطا.

تراوحت أعمار المرضى من ٢٦ إلى ٦٩ وكانت أعمارالمرضى الذين عمرهم ٦٥ فيما أقل ٥٤٪ والأكثر من ٦٥، ٤٦٪ وكانت نسبة الذكور أكثر من الإناث فكانت نسبة الذكور ٦٦٪ ونسبة الإناث ٣٤٪.

وكانت نسبة المدخنين ٦٠٪ من جملة المرضى والغير مدخنين ٤٠٪. وقد تقييم درجة الأداء للمرضى حسب المعدل المعتمد من اللجنة الأوربية للأورام فالمرضى ذوى درجة الأداء (صفر) كانت نسبتهم ٣٠٪ وذوى درجة الأداء (١) كانت نسبتهم ٤٧٪ وذوى الأداء (٢) كانت نسبتهم ٢٣٪.

وطبقاً لأنواع الخلايا المرضية (الباثولوجى) فإن عمق الورم ٥٧٪ من الحالات من الدرجة الثانية، وفى ٦٪من الحالات كان عمق الورم من الدرجة الثالثة، وفى ٣٧٪ من المرضى كان عمق الورم من الدرجة الرابعة. وكانت الغدد الليمفاوية موجبة فى ٦٧٪ من المرضى وسالبة فى ٣٣٪ <.

وقد تم أختبار (hENT1) فى العينات الشمعية فى المرضى عن طريق التحليل المناعى الكيميائى وكانت النتائج كالتالى: كان الناقل عالى الإستجابة فى ٦٣٪ من الحالات وضعيف فى ٣٧٪ من الحالات.

أظهرت الدراسة أن ٤٤٪ من الحالات أظهروا أستجابة جزئية للعلاج و ٢٦٪ من الحالات أظهروا تقدم فى المرض،٢٠٪ من الحالات أظهروا عدم أستجابة وذلك بعمل الفحوصات التقيمية بعد أنتهاء العلاج الكيميائى.

بينت الدراسة أن عوامل التنبؤ بنتائج العلاج التى ثبت أن لها إيجابية إحصائية هى درجة تقييم إيجابية الناقل النيكلوزى المكافئ.

وبعد متابعة المرضى لمعرفة الفترة الإجمالية للحياة (وكان متوسط المتابعة هو ٢٤ شهراً) وجدنا أن ١٠٪ المرضى من حدث لحم وفاة.

المرضى ذو التعبير الهستوكيميائى المناعى للناقل البشرى النيكلوزى المكافئ الضعيف أظهروا مرة حياة كلية أقصر من المرضى ذو التعبير قوى الإيجابية وكان هذا الإختلاف قوى إحصائياً.

\التوصيات: زيادة تعبير الناقل البشرى النيكلوزى المكافئ مصاحب بإستجابة قوية للعلاج ويؤثر إيجابيا فى فترة الحياة الكلية للمريض وفترة الخلو من المرض.

من الممكن أن يلعب (hENT1) درو هام كعامل تنبؤى فى أختيار العلاج الكيميائى لسرطان البنكرياس المتقدم. يجب أجراء دراسة عشوائية تحتوى على عدد أكبر من الحالات وتستمر لمدة أطول وتتضمن دراسة جينية لتحديد دور (hENT1) فى أختيار العلاج الكيميائى فى أورام البنكرياس وأستجابة الورم للعلاج ومدة الحياة الكلية وفترة الخلو من المرض.