Original Article

The Clinico-epidemiologic Characteristics of Iraqi Patients with Neuroendocrine Tumors and Their Response to Long Acting Octreotide

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Abstract:

Background: The lack of studies regarding the neuroendocrine tumors (NET) is related to the rarity of these tumors .Long acting Octreotide is an established treatment for NETs by both providing symptomatic relief & inhibiting tumor growth. However, studies regarding incidence of NETs & their response to long acting Octreotide are still insufficient.

Objectives: To study the clinico-pathologic characteristics of Iraqi patients with NET & their response to long acting Octreotide.

Patients & methods: This is a cross-sectional observational study that was conducted in Oncology teaching hospital using patients' follow-up records. Data recruitment included all NET patients diagnosed after October 2013.

Results: During the study period (2 years) ,38 patients were recorded in Iraq/oncology teaching hospital NET Registry. Patients ` data (age, gender, site of the tumor, metastatic status as well as type of therapy applied) were collected. Twenty one (55.3 %)of the patients were males, M:F=1.2:1 , while 23 patients (60.5%) were over the age of 50 years .The gastroenteropancreatic (GEP) tract being the most common primary site followed by pelvis We found metastatic disease at presentation in 17 (44.7%) of patients and the Liver was the most common metastatic site found in (15.8%, 6 patients). Seventeen (44.7%) patients presented with Grade 3 . Most common therapy applied in our patients included systemic chemotherapy, surgery, long acting Sandostatin & radiotherapy for palliation only according to both NCCN & ESMO guidelines. The median time of remission following Somatostatin analogue (SSA) administration was 3 months compared to 7 months in patients received other modalities of treatment (p=0.003).

Conclusion: Octreotide LAR provides symptomatic response & contributes to disease stabilization & tumor regression in both functional & non functional NETs.

Keywords: Neuroendocrine tumors; somatostatin analogues; chromogranin ; sandostatin.

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Introduction:

NETs are thought to arise from cells throughout the diffuse neuroendocrine system that is composed of peptide- and amine-producing cells. They compromise a broad family of tumors, the most common of which are carcinoid tumors (most commonly arise in the lungs & bronchi, small intestine,appendix, rectum& thymus)& pancreatic NET. Other neuroendocrine tumors arise from parathyroid, adrenal, pituitary gland, & in calcitonin-producing cells of the thyroid (causing medullary thyroid carcinoma). The incidence of gastrointestinal (GI) NETs is 6.2 per 100,000 populations and has been steadily increasing. The increasing incidence of NETs reported in many studies is likely multifactorial and includes increased awareness and improved endoscopic methods of detection.(1) The overall 5-year survival rate of all patients with GIT NETs is 28.5%.(2) Of all NETs ~25% are located in the respiratory tract.

The prevalence of thymic NET is ~3% of the total number of NETs at all sites. The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years. (3) The incidence of Grade1(G1)NET increased from 2.0 to 3.0; there was a large increase in Grade 2(G2) NET from 0.01 in 1990 to 0.2 in 2010, and of the Grade 3(G3) large cell NET from 0.01 to 1.8, respectively. In Grade (3) small cell NET incidence in men decreased from 21.3 to 10.1, whereas in women it increased from 4.5 to 7.7. (4). Tumors fall into one of the following three grades: G1: well differentiated, low grade G2: moderately differentiated, intermediate grade G3: poorly differentiated, high grade. (5) Immuno-histochemical detection of CgA(Chromogranin A) represents the milestone in the diagnostic work-up of NETs. Elevated CgA levels have been found in functioning as well as non-functioning tumours, making it a universal marker in NETs. CgA has recently been described to be predictive of survival and of treatment response in NETs. . Its levels may correlate with the tumour burden, tumour progression or regression in response to therapy. (6) If feasible, the treatment of choice for

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carcinoid tumors is surgical excision. When total resection is not possible, debulking may provide symptomatic relief. If metastasis of carcinoid tumor has occurred and in cases where surgical excision is not suitable, consider treatment with currently recommended chemotherapy. (5) Sandostatin(SST) analogues remain the main symptomatic therapeutic modality for the management of NETs. While decrease in tumor size rarely occurs, the recent PROMID study using octreotide LAR demonstrates a clear effect on time to tumor progression compared with placebo and tumor disease stabilization. The decrease in biochemical tumor markers is evident in about 50 %. (7) Octreotide LAR(SST analogue) treatment provides a sustained symptomatic response in about half of the patients with malignant carcinoid syndrome and contributes to disease stabilization for a longer period (8).

Patients & Methods: The design of the study was cross sectional observational study. A dedicated database including follow-up sheet was built.This survey was conducted in The Oncology Teaching Hospital and recruitment of NET patients` data included (age ,gender ,site of the tumor ,metastatic status as well as the therapeutic modalities applied in patients with all types of NETs except small and large cell lung cancer for the period from October 2013 to April 2016.

Statistical analysis:

The Statistical Package for Social Science (SPSS) version 20 was used for data entry and analysis. Graphs and tables (number and percentage) were used to describe the data and suitable non -parametric statistical tests which make no assumptions about the probability distributions of the variables were used accordingly P value < 0.05 was considered significant.

Results:

During the study period, 38 patients (mean age 50 years old) were recorded in the oncology teaching hospital NET Registry. Of these, 21 (55.3 %) (Mean age 50 years old), were males. The clinicopathologic characteristics are shown in Table 1. Of the 38 evaluable patients, 17 (44.7%) had metastasis, most commonly to the liver (6 patients, 15.8%). Regarding therapeutic intervention, long acting sandostatin (LAR) was administered to 20 patients (52.6%), chemotherapy was given to 23 paients (60.5%) while radiotherapy was given to 3 paients only (7.9%). After a study period of 2 years, a statistically significant difference (p=0.003) in median time to response to treatment was found between the group of patients received Octreotide(20/38) & patients received other modalities of treatment(18/38). Only 2 patients had progression while using Sandostatin & required additional therapy. During the follow-up period of the registry and at the time of analysis, 2 deaths (end stage patients) were documented, corresponding to (5.3%) of the registry population.

Table (1): shows clinicopathological characteristics of the study group

variables		No.	%
age groups/years	<50	15	39.5%
	≥50	23	60.5%
Gender	Male	21	55.3%
	Female	17	44.7%
Site of cancer	Pancreas	10	26.3%
	Small intestine	5	13.2%
	Colon	3	7.9%
	Anus	1	2.6%
	lung	5	13.2%
	Mediastinum	4	10.5%
	Pelvis	6	15.8%
	Breast	2	5.3%
	Larynx	2	5.3%
Grade	G1	5	13.2%
	G2	16	42.1%
	G3	17	44.7%
Metastastatic status	Yes	17	44.7%
	No	21	55.3%
Metastastatic site	lung	4	10.5%
	liver	6	15.8%
	LN	2	5.3%
	Others	4	10.5%
History of surgery	Yes	17	44.7%
	No	21	55.3%
SAS-LAR	used	20	52.6%
	Not used	18	47.4%
Chemotherapy status	Yes	23	60.5%
	No	15	39.5%
Radiotherapy status	Yes	3	7.9%
	No	35	92.1%
Outcome	A live	36	94.7%
	Died	2	5.3%

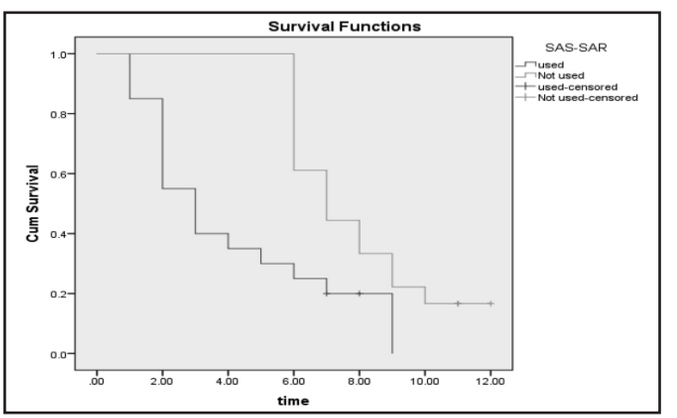

Fig.5.1: Kaplan-Meier curve demonstrates time of response to SAS-LAR compared to other modalities of treatment.

Table 5.2- mean and median of time of response (remission of disease) according to octreotide status.

SAS-LAR	Mean				Median				p-value
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound			Lower Bound	Upper Bound	
used	4.100	.666	2.794	5.406	3.000	.730	1.569	4.431	0.003
Not used	7.944	.512	6.941	8.948	7.000	.703	5.623	8.377	

a. Estimation is limited to the largest survival time if it is censored.

Discussion:

This study represents the 1st attempt to register NET patients in medical city complex, focusing on the epidemiologic and clinico-pathologic characteristics as well as the therapeutic modalities applied in patients with all types of NETs except small and large cell lung cancer. Only few cancer NET registries exist in the USA and Europe, mostly national. According to the SEER database (seer.cancer.gov website), that includes information on 7,262,696 cancer patients, covering for 28 % of the USA population the incidence of NETs in 2004 is 5.25/100.000 inhabitants. On the other hand, data on the incidence of NETs in Europe is limited and is usually reported by anatomic location, most commonly GEP NETs (9). In our registry, 23 patients (60.5%) were over the age of 50 years with male to female ratio (1.2:1). These findings were in accordance to those reported in other published registries (9, 10). We found that the gastroenteropancreatic tract being the most common followed by pelvis. This is slightly different from reported data with pancreas and lung being the commonest primaries, where it was found that 58 % were GEP-NETs, 27 % lung-NETs (11,12). This difference is probably due to the fact that data collected for lung NET is separated from that collected for mediastinal in our registry, the summation of both makes them the 2nd most common site. With respect to the GI tract we found that the pancreas (26.3 %) was the commonest primary site. These results are similar to an Italian study (13) &a study from Middle East & pacific Asia. (11, 12) Seventeen (44.7%) of our patients had metastatic disease at presentation, which is different from a reported Greek study (9).This is may be due to late presentation of our patients. Liver (15.8%) was the most common metastatic site. The data available regarding GEP-NET only with the liver being the most common site of metastasis (2). Notably, 17(44.7%) of our patients presented with G3 disease & 5 patients (13.2%) with G1. With respect to the differentiation grade we could find only one study that reported a 52 % of well differentiated neuroendocrine tumors (NETs) and a 13 % of poorly differentiated NET (9). Descriptions regarding the Ki-67 LI and differentiation grade are lacking in the published NET registries and this is due not only to the

Frequent change in the classification system but also to the underreporting of the Ki-67 in the histological diagnosis. (14) The clinical (symptomatic) response in studies with s.c. octreotide and octreotide LAR is approximately 70% for diarrhoea and flushing; however, previously there have been no long-term data regarding the duration of response. (15) Somatostatin analogs (SSA), octreotide 30 mg, was administered to 20 (52.6%) of the patients for 2 years. After a study period of 2 years, 10 (50%) of the patients had response 3months after initiation of treatment with Sandostatin analogue. The response was documented either by CgA level reduction in 4(10.5%) of the patients or clinically in 14(36.8%) of the patients or both in (39.5%) of the patients. Symptoms were well controlled. No significant adverse effects were noted. This discrepancy between clinical (symptomatic) and biochemical response could be explained by the facts that plasma CgA largely reflects the tumour load, which remains unchanged most of the time, during treatment with somatostatin analogues, despite any clinical response. (7) This is compared to7 months that was required for 50% of the patients received other modalities of treatment to achieve response (p=0.003). These findings are slightly similar to findings from previous data (16) with differences in: 1-not all of our patients have metastasis, 2- our patients have different sites of tumor origin. Studies with larger no. of patients are required to be comparable. Radiotherapy was given to only 3 (7.9%) of the patients for palliative intent. (1,17). Limitations of our study include a) the fact that not all NETs diagnosed in our country between October 2013 and April 2016 were included in the present registry and b) due to few no. of deaths observed survival analysis was not confirmatory.

Conclusion :

Octreotide LAR signficantly lenghtens time to tumor progression , provides a sustained symptomatic response and contributes to disease stabilization for a longer period in patients with functionally active and inactive NETs.

However, studies with larger no. of patients and longer periods of follow-up are still required .

Author's Contributions:

Marwah K. Abdulfattah: Student

Manwer A. Al-naqqash: Supervisor

References:

1-NCCN guidelines 2016.Neuroendocrine Tumors (version 1.2015):MS-2.[internet].available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

2- DeVITA, Hellman & Rosenbergs. Cancer Principles & Practice of Oncology. 10 th edition. United States of America. Wolters Kluwe.2015 .P 1218.

3-K. Öberg, P. Hellman, P. Ferolla, M. Papotti and on behalf of the ESMO Guidelines Working Group. Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [internet]2012; 23 (suppl 7): vii120-vii123. doi: 10.1093/annonc/mds267.Available from: [http://m.annonc.oxfordjournals.org/content/23/suppl_7/vii120.full]

4-Korse CM, Taal BG, van Velthuysen ML, Visser O. -Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer.[internet].1990 [cited 2013May] ;49(8):1975-83. doi: 10.1016/j.ejca.2012.12.022. Epub 2013 Jan 23.available from: [http://www.ncbi.nlm.nih.gov/pubmed/23352435].

5- Evan S Ong. Neuroendocrine Tumors Guidelines .Medscape [internet] [updated Jul 27, 2015].available from: [http://emedicine.medscape.com/article/2500010-overview#a2].

6-Roberta Elisa Rossi, Jorge Garcia-Hernandez, Tim Meyer, et al. Chromogranin A as a predictor of radiological disease progression in neuroendocrine tumours. Ann Transl Med [internet] 2015 Jun; 3(9): 118. doi: 10.3978/j.issn.2305-5839.2015.04.23. available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4481369/

7- C. TOUMPANAKIS, J. GARLAND, L. MARELLI et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. Alimentary Pharmacology & Therapeutics

Volume 30, Issue 7, pages 733–740, October 2009 [internet] version of Record online: 2 JUL 2009 DOI: 10.1111/j.1365-2036.2009.04083.x. available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2009.04083.x/full

8- Toumpanakis C[1], Garland J, Marelli L, et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. Aliment Pharmacol Ther. [internet] 2009 Oct;30(7):733-40. doi: 10.1111/j.1365-2036.2009.04083.x. Epub 2009 Jul 2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19573169.

9- George C. Nikou, Kalliopi Pazaitou-Panayiotou, Dimitrios Dimitroulopoulos, et al. Results of a prospective multicenter neuroendocrine tumor registry reporting on clinicopathologic characteristics of Greek patients. BMC Endocr Disord. 2016; 16: 8.[internet] Published online 2016 Feb 12. doi: 10.1186/s12902-016-0089-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752769/#CR12.

10- Tsai HJ, Wu CC, Tsai CR, et al. The epidemiology of neuroendocrine tumors in Taiwan: a nation-wide cancer registry-based study. PLoS One.2013;8:e62487. doi: 10.1371/journal.pone.0062487.available from: http://www.ncbi.nlm.nih.gov/pubmed/23614051.

11- Yao JC, et al. J Clin Oncol.2008;26:3063-3072.

12- Hwang T, et al. Presented at: 8thAnnual ENETS Conference; March 9-11, 2011; Lisbon, Portugal. Abstract C48.

13- Faggiano A, Ferolla P, Grimaldi F et al. Natural history of gastro-entero-pancreatic and thoracic neuroendocrine tumors. Data from a large prospective and retrospective Italian epidemiological study: the NET management study. J Endocrinol Invest. 2012;35:817–23. [PubMed]. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/22080849.

14- George C. Nikou, Kalliopi Pazaitou-Panayiotou, Dimitrios Dimitroulopoulos et al. Results of a prospective multicenter neuroendocrine tumor registry reporting on clinicopathologic characteristics of Greek patients. BMC Endocr Disord. 2016; 16: 8.[internet] Published online 2016 Feb 12. doi: 10.1186/s12902-016-0089-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752769/#CR12.

15- Plöckinger U, Wiedenmann B. Neuroendocrine tumors. Biotherapy. Best Pract Res Clin Endocrinol Metab 2007; 21: 145–62

16- Pape UF, Berndt U, Müller-Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2008; 15: 1083–97.

17- K. Öberg, P. Hellman, P. Ferolla, M. Papotti. Neuroendocrine Bronchial and Thymic Tumours: ESMO Clinical Practice Guidelines. . Ann Oncol 2012 [internet] ; 23 (Suppl 7): vii120-vii123. . Available from:http://www.esmo.org/Guidelines/Neuroendocrine-Tumours/Neuroendocrine-Bronchial-and-Thymic-Tumours.