Journal of Multiple Sclerosis

Utku and Pape, J Mult Scler 2016, 3:4
DOI: 10.4172/2376-0389.1000193

Letter to Editor OMICS International

Neuroendocrine Tumors

Nalân Utku[1*] **and Ulrich Frank Pape**[2]

[1]*Campus Virchow Institute for Medical Immunology, Institutsgebäude Süd Föhrer, 213353 Berlin, Germany*

[2]*Campus Mitte and Virchow, Charité Comprehensive Cancer Center and Gastrophatology2, Charite, Berlin, Germany*

[*]**Corresponding author:** Nalân Utku, Campus Virchow Institute for Medical Immunology, Institutsgebäude Süd Föhrer, 213353 Berlin, Germany; E-mail: nalan.utku@charite.de

Received date: September 08, 2016; **Accepted date:** December 13, 2016; **Published date:** December 20, 2016

Letter to Editor

There are hormone-secreting neuroendocrine cells scattered throughout the body, known as the diffuse endocrine system (DES). The cells are found singly or in clusters, for example the islets of Langerhans in the pancreas, or the neuro-epithelial bodies found in the broncho-pulmonary tract. The role of many of the neuroendocrine cells is not yet clear; however, some of the gut-based DES cells regulate secretion, absorption, motility, and mucosal proliferation [1].

Neuroendocrine tumors (NETs) are rare, and may be benign or malignant neoplasms of these neuroendocrine cells. They share structural, molecular and functional similarities to nerve cells and hormone-producing cells.

Examples of NETs include: typical and atypical carcinoid tumors, large and small cell neuro-endocrine carcinomas of the lung or thymus, neuroendocrine tumors of the gastrointestinal tract, pancreatic neuroendocrine tumors, medullary thyroid carcinomas, merkel cell carcinomas, pheochromocytomas of the adrenal gland, and paragangliomas. It is estimated that about 64% of NETs originate from the gastro-enteropancreatic system and 28% from the broncho-pulmonary system.

The incidence of NETs has increased significantly in the US, from 1.09 per 100,000 individuals in 1973 to 5.25 per 100,000 individuals in 2004, a rise that has also been observed in other regions of the world.

Current therapeutic options are three fold: surgery and locally ablative treatments; radiation therapy; and systemic medical approaches including chemotherapy and of immunotherapies.

Resection, either through keyhole or more often, open surgery, is the main treatment for all neuroendocrine neoplasms and the only one that can be curative. This is most commonly used in early local or locoregional disease, but may also apply in some cases of metastatic disease.

Radiation therapy can be used locally, for example external beam radiation to individual tumors or systemically, such as somatostatin receptor-mediated radionuclide therapy in gastro-enteropancreatic or broncho-pulmonary NETs or metaiodobenzylguanidine (MIBG)-meditated therapy in pheochromocytomas and paragangliomas.

The possibility of using drugs to treat NETs is undergoing a rapid change with the development of novel therapies.

New therapies that target the vascular endothelial growth factor (VEGF) pathway, which is primarily expressed in vessels, could take treatment beyond that of the established cytotoxic therapies. VEGF and its receptor are expressed at increased in neuroendocrine tumors, providing a rationale to study anti-angiogenic agents to treat NETs.

There are other potential approaches to the treatment of NETs. The serine threonine kinase, rapamycin (mTOR), functions downstream of a number of receptor tyrosine kinases and seems to play an important role in cell growth. These mTOR inhibitors also represent a class of targeted agents and there appears to be early evidence of activity in neuroendocrine tumors.

Supported by the evidence that mTOR inhibitors seem to be active in neuroendocrine tumors, the tyrosine kinase/PI3-kinase/AKT/mTOR cell signaling pathway might be a promising therapeutic approach. Further new agents include inhibitors of IGF1-R and PI3-Kinase, which target different aspects of this same pathway.

Everolimus and sunitinib, two drugs that have been introduced for the treatment of NETs, target these pathways [1,2]. Studies have successfully demonstrated benefit for patients, especially those with pancreatic neuroendocrine tumors and these drugs have become established regimens in NETs.

NETs express high levels of somatostatin receptors. Somatostatin analogs are an additional therapeutic focus. These have traditionally been used as first line treatment for NETs that are symptomatic with hormone hypersecretion. They have also been approved for tumor growth control. In addition to this, somatostatin shows efficacy in controlling symptoms. This therefore suggests the possibility of using radiolabeled somatostatin analogs [3]. A range of phase I, II and III studies of different radio-peptides incorporating indium-111, yttrium-90, or lutetium-177 have resulted in biochemical and radiologic responses [4-11].

Cytotoxic chemotherapy still plays a role in treating selected patients with NETs, particularly pancreatic NETs. It is also useful in the treatment of high-grade neuroendocrine carcinomas of the gastroenteropancreatic system or large and small cell neuroendocrine carcinomas of the bronchopulmonary system.

Platinum-based combination chemotherapy regimens (e.g. cisplatin and etoposide or FOLFOX) have long been used in patients with poorly differentiated and highly proliferative neuroendocrine carcinomas (G3) of any primary tumor location. However, some patients experience considerable long term, and sustained tumor growth control beyond 6 to 12 months is rare.

In contrast, patients with well or moderately differentiated (G1/2) pancreatic NETs respond rather to streptozocin-based regimens. This is currently the only FDA-approved cytotoxic drug with the potential of clinical remission for this indication [12].

Newer approaches to chemotherapy include regimens incorporating the oral prodrug temozolomide alone or in combination with capecitabine. These may provide an alternative approach to systemic therapy, with a promising potential for induction of morphological and

clinical remission. These approaches are in ongoing clinical studies [13,14].

The immune response shown in cancers, triggered by tumor-associated antigens (TAA), is receiving increasing attention [15,16]. Immune-oncological treatment options have raised attention, as cancer patients have a decreased Th1-type immunity, preventing an efficient anti-tumor response. Tumor infiltrating lymphocytes (TIL) allow cancer cells to sustain proliferative signaling, avoid immune destruction and cell death, promote invasion and metastasis, and induce angiogenesis [17].

The role of immunity in NETs is supported by the observation that lymphocyte infiltration is frequently seen in NETs, shown by the results from immunohistochemistry for CD3 (a general T lymphocyte marker), CD4 and CD8 [18-20]. In the analysis of a large case series, 68% of 87 well-differentiated pancreatic NETs were infiltrated by CD3+ T cells. In a study where patients with intermediate-grade tumors were followed up for more than 5 years following surgical resection, CD3+ T cell infiltration was observed to be a significant univariate predictor of improved recurrence-free survival [21]. In 39 resected NET liver metastases, CD3+ cells infiltrated 97% of samples. The pancreas was the most common verified primary site [21].

T cells, especially specific CD8+ T cells targeting carcinoid (i.e., NET) tumor-associated antigens (TAA), have been seen in patients with midgut carcinoid tumors [21,22]. The highest level of CD8+ T cell recognition was for the TAA CgA, suggesting that it has potential as an immunotherapy target. Patients with a low tumor burden showed a significantly higher IFN-γ secretion by CD8+ lymphocytes in response to TAA [23]. Within dendritic cells (DCs), there is a subpopulation of cells that has natural killer properties (CD56 positivity, direct cell lysis via tumor necrosis factor-related apoptosis-inducing ligand, activation of T cells). These cells can be generated *in vitro* when monocytes are incubated with IFN-alpha (IFN-α) [23]. The characteristic of the precursors of the DCs is the upregulation of costimulatory molecules involved in T cell activation, as well as the cytolytic activity toward tumor cells when they are stimulated with IFN-α [24]. In a study of NET patients and healthy controls, significantly more CD14+/CD56+ monocytes were reported in four NET patients than in in the controls. The CD14+/CD56+ monocyte subset was represented >5% of all monocytes in three cases [25].

One of the key steps in the development of immune therapy was the introduction of interferon (IFN)-alpha for the treatment of NETs. IFN-alpha acts by directly inhibiting NET cell cycle progression and hormone synthesis. This reduces neoangiogenesis and activates immune cells [25]. Alterations in HLA class I expression has been seen in pancreatic NETs. This results in missing presentation of TAA-derived peptides to T cells, which is likely to support the development of NETs. These findings led to the hypothesis that TIL are capable of extravasation in inflamed tumors but are blocked by mechanisms of immune suppression that prevent the immune system from eliminating the tumor cells. This immune suppression may be achieved through indoleamine-2,3-dioxygenase [26], programed cell death ligand 1 (PD-L1) and fork head box P3 (FoxP3), which are expressed in regulatory T cells (Treg). In non-inflamed cells, T cell migration is defective [27].

The finding that patients with X-linked hyper-immunoglobulin M syndrome (XHIGM), a primary immunodeficiency disorder with defective B- and T-cell functioning, develop NETs provides indirect evidence that a functional immune system suppresses growing NETs, and that the immune system plays a role in the development of NETs [28].

Expression profiling of tumors suggests that there are at least two different subsets of tumor cells. One is an 'inflamed' subset, where the cells produce innate immune cell molecules. These molecules play a role in effector T cell recruitment that inhibits the immune response. The second is a 'non-inflamed' phenotype. These cells express high levels of angiogenesis-associated factors as well as macrophages and fibroblasts [1].

Increased numbers of intra-tumor mast cells seem to predict shorter duration of survival in Merkel cell carcinoma. This may be because mast cells also play a role in triggering immunosuppression, as well as promoting extracellular matrix degradation angiogenesis and tumor proliferation [29].

The levels of expression of VEGF in tumor tissue can be inversely correlated with the presence of TIL. This negatively regulates antigen presentation by DC and in turn, favors the activity of regulatory T cells [26]. It also triggers T cell apoptosis, which supports the maintenance of immunosuppression in the tumor microenvironment.

TIL are prognostically important in a number of different cancers; for example, their presence and levels can help to improve outcomes in hepatocellular carcinoma [12,13] colorectal cancer [14,15,30,31] and ovarian cancer [32]. However, their use in stratifying individuals with neuroendocrine tumors is not yet clear.

High levels of T regulatory (Treg) cell infiltration seems to be a sign of progression and diminished immune response against the tumor, and increased Treg and tumor infiltration is correlated with reduced patient survival [33]. A number of studies show higher levels of Treg cells in cancer patients, in their peripheral blood and tumor tissue. Like many other cancers, NETs are able to escape the immune response and avoid immunosurveillance via a number of different routes [16].

Suppression of the intrahepatic immune response may have a negative impact on patient survival; this is supported by the observation of a link between higher levels of FoxP3+ cells or Treg and decreased survival in NETs [34]. However, a study carried out in 87 patients with NETs and 39 with NETs with liver metastasis by Katz et al saw a higher CD3+ infiltrate among those with intermediate-grade NETs. This suggested a lower likelihood of recurrence, and implied that there was a benefit in an immune response [34]. Thus, a robust presence of TIL is associated with improved OS (overall survival) following resection of intermediate-grade NETs, whereas the presence of more Treg correlated with shorter OS after treatment.

Tregs in peripheral blood also seem to play a role in tumor progression. In a clinical trial, there was a significant increase in Tregs in patients suffering from carcinoid tumors [20] in comparison with controls.

The serum levels of chromogranin A (CgA) are increased in patients with various chronic inflammatory diseases. Based on this, there is a suggestion that the inflammatory process activates DES. There are positive correlations between levels of CgA, tumor necrosis factor-alpha (TNF-α) and its soluble receptors, which could mean that TNF-α is the key trigger of neuroendocrine cell activation [35,36].

Interferon-alpha (IFN-α) therapy inhibits NET cell cycle progression and hormone synthesis, reduces neo-angiogenesis, and

activates immune cells [37]. This observation supports the importance of immunity in NETs.

Because of evidence of involvement of immunity in NET progress, researchers are looking at DC vaccination. In this approach, DCs are generated *ex vivo*, loaded with TAA and given back to the patient in order to activate tumor-specific T cells [38]. Initial results of small trials seem promising, but the results will have to be applied to larger numbers of patients in controlled clinical trials to verify and validate the effects observed so far. In summary, immunotherapy might be a promising area to consider for the optimization of treatment of NETs in future studies.

The eligibility of patients for immunotherapy might be restricted to cases with proven evidence of TIL/Treg in tumor tissues as well as confirmation of an 'inflamed' condition in patients with NET. Past studies have demonstrated relevant clinical activity for interferon-alpha and subcutaneous interleukin-2 in selected neuroendocrine tumors [39-42].

Recent advances in targeting of CTLA-4 and PD-1 provide opportunities for future advances. Biomarker identification (e.g. cytokines) for patient selection, response prediction and therapy monitoring may be of additional value to establish the potential and promising role of immunotherapy for NET.

References

1. Rindi G, Leiter AB, Kopin AS, Bordi C, Solcia E (2004) The "normal" endocrine cell of the gut: Changing concepts and new evidences. Ann N Y Acad Sci 1014: 1-12.
2. EMA (2010) CHMP variation assessment report. Evaluation of medicines for human use.
3. PR news wire (2010) European Commissions Grants Conditional Marketing Authorization to Pfizer`s Sutent (R).
4. Dong M, Phan AT, Yao JC (2012) New strategies for advanced neuroendocrine tumors in the era of targeted therapy. Clin Cancer Res 18: 1830-1836.
5. Armani C, Catalani E, Balbarini A, Bagnoli P, Cervia D (2007) Expression, pharmacology and functional role of somatostatin receptor subtypes 1 and 2 in human macrophages. J Leukoc Biol 81: 845-855.
6. Taniyama Y, Suzuki T, Mikami Y, Moriya T, Satomi S, et al. (2005) Systemic distribution of somatostatin receptor subtypes in human: An immunohistochemical study. Endocr J 52: 605–611.
7. Hagströmer L, Emtestam L, Stridsberg M, Talme T (2006) Expression pattern of somatostatin receptor subtypes 1-5 in human skin: an immunohistochemical study of healthy subjects and patients with psoriasis or atopic dermatitis. Exp Dermatol 15: 950-957.
8. Ferone D, Pivonello R, Kwekkeboom DJ, Gatto F, Ameri P, et al. (2011) Immunohistochemical localization and quantitative expression of somatostatin receptors in normal human spleen and thymus: Implications for the *in vivo* visualization during somatostatin receptor scintigraphy. J Endocrinol Invest 35: 528-534.
9. Ameri P, Gatto F, Arvigo M, Villa G, Resmini E, et al. (2007) Somatostatin receptor scintigraphy in thoracic diseases. J Endocrinol Invest 30: 889–902.
10. Pintér E, Helyes Z, Szolcsányi J (2006) Inhibitory effect of somatostatin on inflammation and nociception. Pharmacol Ther 112: 440-456.
11. Bánvölgyi A, Pozsgai G, Brain SD, Helyes ZS, Szolcsányi J, et al. (2004) Mustard oil induces a transient receptor potential vanilloid 1 receptor-independent neurogenic inflammation and a non-neurogenic cellular inflammatory component in mice. Neuroscience 125: 449–459.
12. Ustinova EE, Gutkin DW, Pezzone MA (2007) Sensitization of pelvic nerve afferents and mast cell infiltration in the urinary bladder following chronic colonic irritation is mediated by neuropeptides. Am J Physiol Renal Physiol 292: F123–F130.
13. Helyes Z, Elekes K, Sándor K, Szitter I, Kereskai L, et al. (2010) Involvement of preprotachykinin A gene-encoded peptides and the neurokinin 1 receptor in endotoxin-induced murine airway inflammation. Neuropeptides 44: 399–406.
14. Razavi R, Chan Y, Afifiyan FN, Liu XJ, Wan X, et al. (2006) TRPV1+ sensory neurons control beta cell stress and islet inflammation in autoimmune diabetes. Cell 127: 1123–1135.
15. Helyes Z, Elekes K, Németh J, Pozsgai G, Sándor K, et al. (2007) Role of transient receptor potential vanilloid 1 receptors in endotoxin-induced airway inflammation in the mouse. Am J Physiol Lung Cell Mol Physiol 292: L1173–L1181.
16. Schott M (2006) Immunesurveillance by dendritic cells: Potential implication for immunotherapy of endocrine cancers. Endocr Relat Cancer 13: 779-795.
17. Wuttke M, Papewalis C, Jacobs B, Schott M (2009) Identifying tumor antigens in endocrine malignancies. Trends Endocrinol Metab 20: 122-129.
18. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: The next generation. Cell 144: 646-674.
19. Ryschich E, Autschbach F, Eisold S, Klar E, Buchler MW, et al. (2003) Expression of HLA class I/II antigens and T cell immune response in human neuroendocrine tumors of the pancreas. Tissue Antigens 62: 48-54.
20. Vikman S, Sommaggio R, De La Torre M, Oberg K, Essand M, et al. (2009) Midgut carcinoid patients display increased numbers of regulatory T cells in peripheral blood with infiltration into tumor tissue. Acta Oncol 48: 391–400.
21. Katz SC, Donkor C, Glasgow K, Pillarisetty VG, Gönen M, et al. (2010) T cell infiltrate and outcome following resection of intermediate-grade primary neuroendocrine tumours and liver metastases. HPB (Oxford) 12: 674–683.
22. Vikman S, Essand M, Cunningham JL, de la Torre M, Oberg K, et al. (2005) Gene expression in midgut carcinoid tumors: Potential targets for immunotherapy. Acta Oncol 44: 32-40.
23. Vikman S, Giandomenico V, Sommaggio R, Oberg K, Essand M, et al. (2008) CD8+ T cells against multiple tumor-associated antigens in peripheral blood of midgut carcinoid patients. Cancer Immunol Immunother 57: 399-409.
24. Papewalis C, Jacobs B, Wuttke M, Ullrich E, Baehring T, et al. (2008) IFN-alpha skews monocytes into CD56+-expressing dendritic cells with potent functional activities *in vitro* and *in vivo*. J Immunol 180:1462–1470.
25. Papewalis C, Jacobs B, Baran AM, Ehlers M, Stoecklein NH, et al. (2011) Increased numbers of tumor-lysing monocytes in cancer patients. Mol Cell Endocrinol 337: 52-61.
26. Oberg K, Ferone D, Kaltsas G, Knigge UP, Taal B, et al. (2009) Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society: ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Biotherapy. Neuroendocrinology 90: 209–213.
27. Pschowski R, Pape UF, Fusch G, Fischer C, Jann H, et al. (2016) Increased activity of the immunoregulatory enzyme indoleamine-2,3-dioxygenase with consecutive tryptophan depletion predicts death in patients with neuroendocrine neoplasia. Neuroendocrinology 104: 135-144.
28. Gajewski F, Fuertes M, Spaapen R, Zheng Y, Kline J (2011) Molecular profiling to identify relevant immune resistance mechanisms in the tumor microenvironment. Curr Opin Immunol 23: 286-292.
29. Erdos M, Garami M, Rákóczi E, Zalatnai A, Steinbach D, et al. (2008) Neuroendocrine carcinoma associated with X-linked hyper-immunoglobulin M syndrome: Report of four cases and review of the literature. Clin Immunol 129: 455–461.
30. Beer TW, Ng LB, Murray K (2008) Mast cells have prognostic value in Merkel cell carcinoma. Am J Dermatopathol 30: 27-30.

31. Helyes Z, Pintér E, Németh J, Sándor K, Elekes K, et al. (2006) Effects of the somatostatin receptor subtype 4 selective agonist J-2156 on sensory neuropeptide release and inflammatory reactions in rodents. Br J Pharmacol 149: 405–415.
32. Varecza Z, Elekes K, László T, Perkecz A, Pintér E, et al. (2009) Expression of the somatostatin receptor subtype 4 in intact and inflamed pulmonary tissues. J Histochem Cytochem 57: 1127–1137.
33. Chowers Y, Cahalon L, Lahav M, Schor H, Tal R, et al. (2000) Somatostatin through its specific receptor inhibits spontaneous and TNF-alpha- and bacteria-induced IL-8 and IL-1 beta secretion from intestinal epithelial cells. J Immunol 165: 2955–2961.
34. Vikman S, Sommaggio R, De La Torre M, Öber K, Essand M, et al. (2009) Midgut carcinoid patients display increased numbers of regulatory T cells in peripheral blood with infiltration into tumor tissue. Acta Oncol 48: 391-400.
35. Katz SC, Pillarisetty V Bamboat ZM, Shia J, Hedvat C, et al. (2009) T cell infiltrate predicts long-term survival following resection of colorectal cancer liver metastases. Ann Surg Oncol 16: 2524-2530
36. Sciola V, Massironi S, Conte D, Caprioli F, Ferrero S, et al. (2009) Plasma chromogranin a in patients with inflammatory bowel disease. Inflamm Bowel Dis 15: 867-871.
37. Di Comite G, Marinosci A, Di Matteo P, Manfredi A, Rovere-Querini P, et al. (2006) Neuroendocrine modulation induced by selective blockade of TNF-alpha in rheumatoid arthritis. Ann NY Acad Sci 1069: 428–437.
38. Oberg K, Ferone D, Kaltsas G, Knigge UP, Taal B, et al. (2009) Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society: ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Biotherapy. Neuroendocrinology 90: 209–213.
39. Weinstock JV, Elliott D (2000) The somatostatin immunoregulatory circuit present at sites of chronic inflammation. Eur J Endocrinol 143: S15–S19.
40. Prasse A, Zissel G, Lützen N, Schupp J, Schmiedlin R, et al. (2010) Inhaled vasoactive intestinal peptide exerts immunoregulatory effects in sarcoidosis. Am J Respir Crit Care Med 182: 540–548.
41. Pozo D, Anderson P, Gonzalez-Rey E (2009) Induction of alloantigen-specific human T regulatory cells by vasoactive intestinal peptide. J Immunol 183: 4346–4359.
42. Vitale D, Lupoli G, Guarrasi R, Colao A, Dicitore A, et al. (2013) Interleukin-2 and Lanreotide in the treatment of medullary thyroid cancer: *In vitro* and *in vivo* Studies. J Clin Endocrinol Metab 98: E1567-E1574.