Neuroendocrine Tumors

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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 or produce digestive hormones 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 analogs or metaiodobenzylguanidine (MIBG)-mediated 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 produg 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 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], programmed 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 immnosuppression 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


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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


