The Patient-Centric Approach to Neuroendocrine Disease

1. Abstract

Neuroendocrine tumors - what we now describe as 'NET cancer' - is a relatively rare disease which is poorly understood and is often misdiagnosed. As recently as 25 years ago, there was no medication and no treatment available other than surgery. But this has changed dramatically with the discovery that neuroendocrine tumors frequently express a high density of receptors which bind somatostatin and various synthetic peptides. This has led swiftly to the evolution of precise imaging techniques and therapy using targeted radiation. From the patients' perspective, a diagnosis of NET cancer is no longer a terminal illness. Today one can view NET cancer as a chronic disease if it is well-managed using a combination of surgical debulking, regular monitoring with receptor-based imaging techniques and properly-staged peptide receptor radiotherapy. The patient journey is ideally one in which they work collaboratively with their specialist physicians to diagnose and treat the disease. The guidance which patients need as they embark on this journey is to seek coordinated multidisciplinary care, ideally from a centre of excellence, and ensure that their treatment follows concensus guidelines. Such patients can live long an productive lives.

2. Article

2.1. Introduction - Disfunction of the Endocrine System

I lead a cancer patient support group based in Singapore which serves the South East Asia region. Our group is focused on neuroendocrine tumors - what we now describe as 'NET cancer'. This is a relatively rare disease which is poorly understood and is often misdiagnosed. Thankfully, with early diagnosis and proper treatment, patients enjoy good prospects for long and productive lives.

In fact, with current medical technology and expertise, NET cancer can be managed as a chronic condition rather than a terminal illness. Prior to 1989, there was no medication and no treatment other than surgery for patients who had neuroendocrine tumors. In that year, Octreotide was approved by the US Federal Drug Administration (1) and became the frontline therapy for NET cancers. It continues to be a drug of choice not because it reduces tumor burden, but because it mitigates some of the common symptoms, including diarrhea and facial flushing.

When I first meet a NET cancer patient or caregiver, I often begin with a discussion of the term neuroendocrine, breaking it down into the respective components: neural and endocrine. Most folks with a high-school biology education will recall that these are anatomical systems of interrelated organs. The neural or nervous system transmits signals to and from the brain. The endocrine system consists of a set of glands which secrete various hormones directly into the blood stream.

These two systems interact because nerve impulses regulate the secretion of hormones. We don't think about this process - it just happens 'autonomically'. For example, there is a part of our anatomy known as the enteric nervous system which is responsible for regulating the process of digestion. Digestion is regulated with hormones secreted by the pancreas, the stomach and intestines. In fact, there are more neural pathways in the

gut than in any other organ except the brain (2). This is often described as the brain/gut connection, a connection we acknowledge with the phrase 'gut feeling'.

Disfunctions of the neuroendocrine system begin with imbalances in hormone levels, which can then precipitate gross physical symptoms. For example, an important gastro-intestinal signal pathway involves endocrine cells which metabolise serotonin (as well as tryptophan and 5-hydroxytryptamine) and these activate motility reflexes. Excessive release of serotonin can cause nausea and vomiting. Severe imbalances in the enteric neuroendocrine system can manifest as chronic illnesses (2), such as: Irritable Bowel Syndrome (IBS), Crohn's disease, diabetes and even neuroendocrine cancer.

But how? By the late-1960s, it had become apparent from pharmacologic studies that opiate drugs were likely to exert their actions at specific receptor sites. In the early 70s, scientists researching these receptors discovered the naturally occuring peptide somatostatin and noted its important role in gastrointestinal functions and disorders (3). It became apparent that chronic illnesses of the gastro-intestinal tract were not just related to chemical imbalance or infections, but that specific signal pathways were reinforcing or even amplifying the disfunctional characteristics.

Five somatostatin receptor cell subtypes were identified and named SST1, SST2 and so on. Pathologists noted that neuroendocrine tumors frequently express a high density of SSTs. Understanding the ability of somatostatin to bind to these SST receptors was a key breakthrough that led directly to the production of the synthetic peptide Octreotide - also know as Sandostatin - the first widely available treatment for NET cancer.

For many years it was assumed that Octreotide's mechanism of action was to interrupt the metabolism of serotonin, reducing secretion of the hormone that caused diarrhea and facial flushing. But it was suspected that there was also an interruption of the signal pathway between the SSTs and the blood capillaries which feed nutrients to tumor cells. If so, Octreotide would be anti-proliferative - it would stop the tumors from growing by muting their ability to shout 'feed me, feed me' to nearby blood vessels. This anti-angiogenic effect was demonstrated in the recent Promid study (4). We now know that Octreotide helps NET cancer patients achieve stable disease, even if they are asymptomatic.

2.2. Misdiagnosis, Delayed Diagnosis and Underdiagnosis

We don't yet know exactly what causes neuroendocrine tumors to arise in the first place. As in all cancers, there is some genetic proclivity and some biological or environmental factors which initially give rise to the tumor (5) (6). There are both familial clusters and geographic clusters mentioned in medical journals. Because neuroendocrine tumors are slow growing relative to other cancers, they can develop over many years and may not be easily identified by physicians.

It is well known that NET cancers are associated with excessive production of serotonin and the signature facial flushing, which over time can result in rosacea. However endocrine tumor cells also have the ability to secrete a variety of other peptides and amines, sometimes with multiple hormones co-secreted from the same cells (7). For example, primary tumors may secrete one type of hormone, while metastases secrete another. This variety of secretions can lead to complex symptoms and confound easy diagnosis: diarrhea can lead to exhaustion and weight loss; fibrosis can lead to

abdominal pain and even heart valve damage; and facial flushing may or may not be present.

These symptoms are often attributed to other gastrointestinal causes, such as irritable bowel syndrome (IBS), Crohn's disease, or peptic ulcer disease (gastric acid reflux) (8); thus, the possibility of NET cancer as a prognosis is frequently overlooked until mass effects arise (9). Many patients report they have been treated for months or years as an IBS patient, only to learn much later that they actually have neuroendocrine tumors.

One patient reported that: "I was hospitalized three times with pain in the area of my appendix. I was told that the pain was either stress-related or IBS. After the third time, I was told never to come back to the hospital again for this… They made me wait in the emergency room (at my next visit); my appendix burst due to a goblet cell carcinoid tumor while I waited 10.5 hours for an operation (12)." Such anecdotes illustrate that patients may not receive timely and appropriate medical attention if the symptoms are not recognized.

Of course, a cancer diagnosis comes as a shock to the patient and is always a life-changing event for them and their family. This is especially true if they have distant metastases such as in the liver. It is natural that they will ask questions such as: "couldn't this disease have been detected earlier, before it spread to my liver"?

In fact there are relatively simple non-invasive means to screen out neuroendocrine patients from the much larger community of those with undiagnosed but chronic gastric problems. Modern radiographic scans are capable of imaging tumors as small as 1cm, though many neuroendocrine primary tumors may be too small to visualise on these scans. Sadly, once they achieve a size of 2cm, they are often metastatic. Chromagranin A (or CgA) is a specialised blood test which can detect most cases of NET cancer and is very reliable if the potential for false positives is mitigated. Even a simple and inexpensive 5HIAA urine test is able to detect an excess of seratonin by-products, which might signal the presence of NET cancer, especially if there are liver metastases.

The education of gastro-intestinal specialists about the availability of such tests is the best means to assure patients that every effort has been taken to provide early and accurate detection. The GI specialist should never take IBS as a final diagnosis, but should keep investigating the causes of chronic gastric illness. In fact, there is a growing body of evidence that IBS itself is due to serotonin imbalances (11).

The difficulty of accurately diagnosing patients has led to under-reporting in the South East Asia region served by our support group. In the United States and Europe incidence is about 5 per 100,000 individuals, whereas it is less than 1 per 100,000 in our region. And in the western countries, the number of patients newly diagnosed each year has increased dramatically in the past 20 years. This increasing incidence is attributed to greater awareness and better diagnostic techniques.

2.3. Engaging a Multidisciplinary Team

Once a diagnosis is confirmed, it is important for the patient to consult with specialist physicians. This is one of the important functions of our support group, to help patients and their family caregivers identify experts who are familar with NET cancer.

Usually we recommend a medical oncologist as the senior consultant to the patient. The oncologist has an overview and grasp of the treatment options that would be appropriate. Oncologists are trained to recognise the unique aspects of NET cancer, such as small primaries and large metastases, which will determine the treatment choices. They provide an important function in monitoring the course of disease, keeping track of biomarkers such as CgA (a key measure of tumor burdon) and getting tissue samples into cancer registries. Oncologists are also very knowledgeable about chemotherapy, even though such treatment is rarely of use for NET cancer patients - except when fighting more aggressive tumors (7) (10).

Usually the next member of the team is a competent surgeon. Surgeons are often specialised in certain parts of the anatomy. For example a hepatobiliary surgeon operates on the pancreas and liver - sensitive organs that general surgeons will carefully avoid. Depending on the extent of disease, it is appropriate to seek guidance from a surgeon specialised in the affected organs.

An endocrinologist will be most familiar with hormone treatments such as Octreotide and with the use of receptor targeting in therapy. If the patient is going to consider targeted radiation therapy, it is essential to get an endocrinologist on the team.

There are a variety of scans which will be helpful in staging and monitoring the extent of disease. These are CT, MRI and specialist scans such as Octreotide SPECT and Gallium 68 (or Ga68) PET/CT. This type of PET scan is different from the normal FDG PET, which is designed to image carcinomas, though such aggressive tumors may co-exist with neuroendocrine cancer and in those cases both PET scans may be required.

As of January 2012, Singapore General Hospital (SGH) nuclear medicine department has been offering the Ga68 PET/CT for two years, and it is regarded as the world's best imaging technique for NET cancer. It can image tumors less than 0.5cm and in addition to indicating tumor size (the CT portion) this scan measures tumor receptor activity in terms of Standard Uptake Values. If procedures are standardized, SUVs can be compared in the same patient over time to determine the effectiveness of treatments.

To get these scans performed and interpreted properly the patient needs to consult a radiologist or imaging specialist from nuclear medicine. After a scan, written reports are sent to the referring oncologist, so it's common that the patient and caregiver do not consult directly with imaging specialists. But oncologists may not be able to interpret the scan beyond simply reading the written report. With permission from the oncologist, a consultation with the imaging specialist can be arranged and is usually very helpful in deciding on the course of treatment.

In addition to the oncologist, surgeon, endocrinologist and imaging specialists, there is a supporting cast of pathologists, hematologists and nurses. The pathologist plays a particularly crucial role, which is to measure the proliferation of tumor cells in tissue excised during surgery or obtained via biopsy. This is done using a procedure called a Ki-67 test which can classify neuroendocrine tumors as low (<2%), medium (2-5%) or high (>5%) grades of malignancy. Obviously, a more aggressive disease needs to be managed differently than an indolent one.

In a hospital which focuses on multidisciplinary care, all these team members assemble for regular meetups known as a 'neuroendocrine tumor board'. It can be extremely helpful to have a patient's case reviewed by the NET cancer tumor board.

Although multidisciplinary care is the best way to manage rare diseases in general and NET cancer in particular, only a small number of hospitals around the world have these tumor boards for NET cancer. If a patient can't get his case referred to one of these boards, it is even more important to ensure that each of the specialists is regularly consulted and that a senior consultant coordinates the communications.

One of the most common questions to our support group is whether the surgeon needs to have experience with NET cancer. Actually no - we recommend selecting a surgeon who is familiar with the affected organs and with cancer surgery in general. But if they are guided by a competent oncologist and radiologist or imaging specialist from nuclear medicine, then that will be more than sufficient.

2.4. Becoming an e-Patient

An online survey conducted by our support group in 2010 found that more than two-thirds (69%) of patients reported traveling outside their state, province, or country for NET-related diagnosis or treatment. A further 11% of those who responded to the survey were considering or planning such travel (12).

Most of the respondents were from USA and Canada, where distances are large and patients in rural communities typically lack specialist care. It was interesting that the reasons given for such travel were not to save money but to obtain better care.

Travelling overseas for specialist medical care is an option Asian patients should consider if they are not able to identify expertise in their own countries. For those living in Singapore, there are a growing number of specialists with experience in treating NET cancer. In addition, institutions like Singapore General Hospital are investing in state-of-the-art services such as Ga68 PET/CT scans and the new Peptide Receptor Radiotherapy using Leutitium (Lu-177). Hopefully patients from around the region will come to Singapore to take advantage of its expertise and specialised services.

However some patients with advanced disease or complex cases may still prefer to go to one of the European medical centres which cater specifically to NET cancer patients. These centers offer multidisciplinary care, see hundreds or even thousands of NET cancer patients each year, and some are recognised internationally as centres of excellence in treatment of neuroendocrine tumors. The lead physicians are typically involved in multi-center medical trials and have usually co-authored a number of articles on NET cancer in prestigious medical journals. These are the super-docs.

Here is a brief list of these European centers, in alphabetical order:

- **Central Clinic, Bad Berka (a small town near Weimar), Germany** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Richard Baum, who heads the department of nuclear medicine. This centre offers Ga68 PET/CT and Peptide Receptor Radiotherapy using a combination of Lu-177 and Y-90, tailored to each patient's treatment needs.

- **Charite University Hospital, Berlin, Germany** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Bertram Wiedenmann. Each year more than 1,600 consultations are given to patients with neuroendocrine tumors. Multidisciplinary treatment is closely coordinated between specialists of the Departments of Surgery, Diagnostic Radiology and Nuclear Medicine and the Institute of Pathology. No PRRT is available at this centre.
- **Erasmus Medical Center, Rotterdam, Netherlands** - The senior physician seeing neuroendocrine cancer patients is Dr. Dik J. Kwekkeboom, who heads the department of nuclear medicine. This centre specializes in Peptide Receptor Radiotheraphy using Lu-177. The use of LU-177 Octreotate as a targeted treatment was pioneered here by Dr. Eric Krenning and Dr. Kwekkeboom.
- **Beaujon Hospital, Clichy (a suburb of Paris), France** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Philippe Ruszniewski, who heads the department of gastroenterology. This centre offers multidisciplinary care including surgery, hepatic arterial embolisation and chemotherapy using novel agents such as Sunitinib and Everolimus.
- **Innsbruck Medical University, Innsbruck, Austria** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Irene Virgolini, who heads the department of nuclear medicine. This centre offers Ga68 PET/CT and Peptide Receptor Radiotherapy using a combination of Lu-177 and Y-90, tailored to each patient's treatment needs.
- **Royal Free Hospital, London, England** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Martyn Caplin, who heads the department of gastroenterology. This centre offers multidisciplinary care including surgery, hepatic arterial embolisation, Peptide Receptor Radiotherapy using a combination of Lu-177 and Y-90, immunotheraphy using Interferon and chemotherapy using novel agents such as Sunitinib and Everolimus.
- **University Hospital (Rigshospitalet), Copenhagen, Denmark** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Ulrich Knigge, who is Clinical Associate Professor in the department of surgery. This centre offers multidisciplinary care and Peptide Receptor Radiotherapy using Lu-177.
- **University Hospital, Basel, Switzerland** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Jan Mueller, who heads the department of nuclear medicine. This centre offers Ga68 PET/CT and Peptide Receptor Radiotherapy using Y-90.
- **University Hospital, Uppsala in Sweden** - The senior physician seeing neuroendocrine cancer patients is Prof. Dr. Kjell Oberg, who heads the endocrine oncology unit. This centre offers multidisciplinary care involving endocrine surgery, pathology, clinical chemistry, radiology, and nuclear medicine. The centre is noted for its expertise in immunotheraphy using Interferon and in specialised treatment for pulmonary neuroendocrine tumors.

Before a patient can be considered for treatment in any of these centres, he or she must provide medical records. The fastest way to deliver this information to a physician is by email or electronic file transfer, and there are free services such as Dropbox (http://dropbox.com) where patients can securely upload large files such as medical imaging scans. The physician will then reply by email, often providing helpful recommendations without charge. It is up to the patient to assemble his or her electronic dossier, and such patients are referred to as e-patients because they are not physically present for the consultation.

It is a good practice for the patient (or a family caregiver if the patient is unable) to assemble all the relevant medical records in electronic form. Here are some tips:

- Request and retain the CDs for any medical scans such as CT, MRI, or PET imaging. These may incur a small cost, but are an important part of the medical record.
- Download a free utility such as Sante Viewer which can open the type of files used in medical imaging (usually these are Dicom images). When sharing medical scans, one can include this viewer on the disc or file transfer without violating any copyrights. Some patients even use this viewer to extract relevant images and copy them into a printable document.
- Scan any medical reports from paper into document files on the computer. The best format for retention and sharing with physicians is Acrobat PDF. To produce these PDFs, an inexpensive utility is available from Software 995 (http://pdf995.com).
- Organise the above documents by date. For example, a CT scan performed on 11 March 2011 would be placed in a folder labelled '20110311_CT'. A blood test report prepared on the same date might be labelled 'blood_results_20110311.pdf'.

With this preparation, the patient is always ready to be assessed by an international specialist or a neuroendocrine board, and the treatment options are limited only by the patient's budget and ability to travel. Be sure that the patient is holding a passport valid for at least the next 6 months.

2.5. Following Concensus Guidelines

Professional medical associations in several parts of the world have established concensus guidelines for the treatment of neuroendocrine tumors. To appreciate the value of concensus guidelines, consider some of the following questions which are likely to pose a dilemma to medical oncologists:

- If a patient is flushing, is it due to pulmonary or mid-gut neuroendocrine disease? [It could be either one - pulmonary NET cancers also cause flushing.]
- If a patient has metastases in the liver, is it too late for surgery to remove the primary located elsewhere? [No, studies have shown that patients benefit from removal of their primary tumors whether or not they have liver mets.]
- Is the goal of NET cancer surgery complete removal of the tumors - what surgeons call an R0 resection? [Not necessarily so. Patients with advanced disease can benefit from debulking even if some residual disease remains.]
- Should Peptide Receptor Radiotherapy only be used if the patient has progressive disease? [Not true, studies have shown that PRRT is more effective if performed early and works best with small distant metastases rather than bulky tumors.]

Clearly neuroendocrine tumors behave differently from carcinomas and other more aggressive cancers. The primary tumors are small and the metastases are large - which is the reverse of other cancers - and is the reason most NET cancer patients are metastatic at diagnosis (7) (10). NET tumors are also more slow-growing or indolent. This is because the cells divide less quickly, with the result that certain scans such as FDG PET don't image these tumors well and chemo therapies may not work.

For these reasons, a medical oncologist needs the guidance of more experienced specialists. This is the function of the concensus guidelines. The guidelines are not a prescription but they are a snapshot of expert opinion on the best diagnostic and

treatment algorithms at the time they are published. They may even be superceded if evidence indicates that a new or novel therapy is better than current practices.

For historical reasons, there are different sets of neuroendocrine cancer guidelines published in Europe, North America, Canada and UK, but they follow one another fairly closely. The two guidelines which are most widely recognised internationally are:

- North American Neuroendocrine Tumor Society (NANETS) Consensus Guidelines for the Diagnosis and Treatment of Neuroendocrine Tumors
- European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors

For patients the greatest benefit of these guidelines is the potential for improving health outcomes. Guidelines that promote interventions of proven benefit and discourage ineffective ones have the potential to reduce morbidity and mortality and improve quality of life (13). Unfortunately, patients and their family caregivers have a difficult time reading scholarly medical papers, so the insights contained in these concensus guidelines can be inaccessible to them.

Medical associations, pharmaceutical companies and patient groups like ours often help by translating the concensus opinion into leaflets or web-based information written in a manner which is easy-to-understand. Such presentations often take the approach of 'Did You Know?' A good example of such a publication for neuroendocrine disease is the NET Alliance website (http://www.thenetalliance.com) produced by Novartis Oncology. Of course, patients should be wary of information that is likely to have a commercial bias and counter-check against other sources.

Since the mid-90s, specialist physicians in North American and Europe have been regularly working with patient support groups to organise patient conferences. These conferences offer an excellent opportunity to hear the unvarnished truth about the best diagnostic approaches, the newest treatment options, and research being done to benefit NET cancer patients. Although corporate sponsors subsidise the cost of these events, they don't influence the content and are rarely invited to promote products.

Said Dr. Gene Woltering who organised one of the first national patient conferences for NET cancer held in USA: "Such conferences represent the cutting edge of medical information dispersal. Getting life saving information to patients with this exceedingly rare disease allows the patient to educate their local doctors rather than the usual paradigm in which physicians are the ones with the knowledge (14)."

These events also provide an opportunity for networking, and for many patients attending such a conference is the first time they will meet others with the same rare disease. That alone is a tremendous value.

If one is not able to attend physically, most of these conferences are also recorded and can be viewed online. Our support group website has links to many such recordings.

2.6. How Support Groups Help

Support groups such as ours serve two functions: (a) assisting diagnosed patients to obtain the best possible care, and (b) promoting awareness of this disease amongst healthcare professionals as well as the wider public. Much of our work is focused on

newly diagnosed patients, providing them with general information, suggesting further tests or treatment options, putting them in touch with specialists and referring cases to a neuroendocrine tumor board. We don't have experience in emotional counseling, but we encourage patients to investigate and seek multiple opinions, rather than worry.

Our group produces seminars and we publish information on the Internet. One of the valuable services we can provide new patients is to connect them with online discussion forums such as the American Cancer Online Resources (ACOR) Carcinoid list. This is an online forum with over 800 members, mostly NET cancer patients and caregivers, who willingly advise other patients based on their experience. This service operates every day, 24 x 7, and it's reassuring to patients that they are able to help one another.

In addition, our group participates in an international alliance of patient activist groups focused on neuroendocrine disease. This alliance organises the NET Cancer Day (http://netcancerday.org) awareness event held each year on 10 November. Its main message is to promote early detection. The alliance members hold regular teleconferences and annual meetups to exchange news of local happenings and share best practices.

3. Conclusion

Neuroendocrine cancer is a rare disease that is often misdiagnosed. Patients - even those with pulmonary neuroendocrine disease - most commonly present with symptoms of gastric distress and elevated hormone secretions in the blood and urine. This means that gastroenterologists are on the front lines and must be armed with the right diagnostics to screen these cancer patients from the background of IBS, Crohn's and other digestive disorders. The index of suspicion must be high if the patient has prolonged IBS-like symptoms without any benefit from standard treatments.

There are a number of diagnostic options including urine and blood tests, but the most accurate and decisive test is a Ga68 PET/CT. This scan can localise very small neuroendocrine primary tumors and determine the extent of metastases (if any). The same test can prequalify a patient for Peptide Receptor Radiotherapy (PRRT) and is useful in monitoring the outcome of such treatment. Singapore General Hospital (SGH) is offering this diagnostic imaging test and has just launched a treatment programme using Lu-177 PRRT.

Because NET cancer is a rare disease, individual physicians don't see many such patients. Compound that with the complexity of the disease, and it's easy to appreciate that multi-disciplinary care is required. Unless the patient has access to a centre of excellence, they must coordinate this multi-disciplinary care on their own.

Our support group tends to encounter patients soon after they are diagnosed. We guide them to identify a medical oncologist as their primary consultant, to seek multi-disciplinary care and to prepare themselves as an e-patient since it is likely they will travel out-of-country for treatment at some stage. We make them aware of concensus guidelines and the availability of review by a neuroendocrine tumor board.

NET tumor disease is sometimes referred to as the 'good looking cancer' because the patients appear outwardly healthy. In fact, with well-coordinated specialist care, they can stay looking healthy and living productive lives for decades.

To some extent, a patient's financial ability and their access to information technology determine quality of care. However it is my observation that the patient must also take a degree of ownership of their health outcomes. This will empower them to communicate with specialists and to make timely and reasonable decisions about their treatment. Patient-centered medicine really begins with the patient having a voice.

I would therefore conclude that the difference between NET cancer patients who do well and those who fare poorly is in part their level of personal engagement. Patients who are engaged with their medical teams and who can avail themselves of the best treatments enjoy a longer and improved quality of life.

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5. Biography

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