Supportive care in the management of Neuroendocrine Neoplasms

Introduction

Improvements in the treatment of neuroendocrine tumours have led to corresponding increases in the number of patients living longer.

Unfortunately, there remain reports of significant delays in diagnosis, with the disease still frequently having progressed to metastatic stages before the diagnosis is made. This has resulted in increasing numbers of patients, many living with metastatic disease and ongoing symptoms which impacts the quality of life, financial stability and psychosocial wellbeing of patients and their families.

This section is in three chapters, focusing specifically on three key areas of supportive care:

Chapter 12: Diet and nutrition

Chapter 13: Psychosocial care

Chapter 14: Exercise and NENs

DRAFT

CHAPTER 13: PSYCHOSOCIAL CARE

Authors: Prof Jane Turner, Kate Wakelin

Practice Points

- Patients with NENs should be advised that attention to their emotional adjustment and needs is an important component of their care.
- All health professionals involved in the care of patients with NENs should participate in communication skills training.
- Clinicians should ensure that patients with NENs have access to plain-language information about their condition and treatment including resources to explain their condition to carers.
- Exploration of the patient's perception of the path to their diagnosis of NENs is recommended, so that treating health professionals are aware of issues such as anxiety and lack of confidence which can affect the patient's engagement in decision-making and treatment.
- Patients should be screened for distress using a structured measure (such as the Distress Thermometer) at diagnosis and when there are changes in disease stage and treatment. Identification of distress should lead to further discussion including the possibility of referral for specialised treatment.
- All clinicians caring for patients with NENs should have established pathways to refer distressed patients to health professionals trained in providing psychosocial support and treatment. Large public hospitals provide access to psychologists and psychiatrists. In private practice the GP is optimally placed to facilitate referral, for example to a community-based psychologist using a Mental Health Care Plan.
- Clinicians should advise patients with NENs about support programs and counselling services.

DRAFT

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of rare cancers that derive from the neuroendocrine cell system. There are several unique aspects of NENs which may shape psychosocial adjustment.

Patients may feel their condition is “less worthy” of medical research and treatment options compared with more common cancers such as breast cancer. The non-specific nature of symptoms makes the diagnosis challenging and almost 50% of patients are diagnosed with another condition before receiving a NENs diagnosis [Wolin 2017]. Significant delays in diagnosis are common, with the median length of time from initial symptomatic presentation to diagnosis 9.2 years [Vinik]. These experiences surrounding diagnosis can result in considerable psychological and emotional burden, contributing to the reported worse health-related quality of life (HRQoL) outcomes among patients with NENs compared with the general population [Singh, Beaumont]. For many patients there can be a breakdown of trust in the health system generally. Patients may doubt the expertise of their health care providers, feeling the need to take on the role of self-advocate, which can be burdensome for many.

Consultations with multiple health professionals with differing opinions potentially further undermines confidence in medical care [Leyden 2018]. Discussion of the diagnosis with friends and family can be challenging as access to “plain English” information is limited, leading to isolation and a sense of not being understood by others. Being an uncommon cancer (with a very different course of disease and treatment to more common malignancies), those diagnosed with NENs may be more prone to social isolation within the supportive care community as well, with sparsely located specialised services, and a potential lack of knowledge and understanding from generalist services that are unaccustomed to managing the specific needs of NENs patients (such as carcinoid heart disease and vitamin deficiency syndromes).

A further challenge for patients is the variation in clinical status and prognosis which ranges from high grade disease (with very poor prognosis) through to very indolent tumours which remain relatively stable, sometimes for decades. Thus the umbrella term NENs can in fact have vastly different implications for the individual and pose different emotional challenges. While the distress associated with aggressive disease is obvious, individuals with indolent tumours may live in fear that their situation could change for the worse.

It is unsurprising that international data reveals high levels of unmet needs, with the majority of advocates considering that patients’ psychological needs were often not met (38%) or not met at all (38%) [Leyden 2019]. The nature and severity of symptoms have a powerful impact on adjustment, with higher symptom burden being associated with higher psychological distress. Patients with GI NENs are more likely to report an adverse social impact [Leyden 2018], perhaps because their symptoms can so profoundly affect daily life and social interactions.

Living with a condition that is neither curable, nor imminently terminal presents unique challenges. Inability to work because of symptoms means more than a financial burden. Work provides opportunities for social interaction, gives a temporal structure to the day, and provides a sense of identity, purpose and achievement. Distress related to being unable to work is likely compounded by the considerable financial impact of tests and treatments for NENs [Gordon]. Socially there can be significant impacts, as the patient and those around them struggle to come to terms with the wearing nature of ongoing uncertainty. Survivorship care (such as rehabilitation) has traditionally focused on those who have completed cancer therapies. For those receiving ongoing treatment, there are additional survivorship issues that need to be addressed, including those surrounding the adherence to ongoing therapy over extended periods of time [Jacobsen].

The broad ranging impact of cancer on caregivers has been thoroughly explored (although there is minimal literature available that describes this in NENs). Amongst

DRAFT

numerous physical, social and economic impacts of this role, Girgis et al [2013] describe factors that increase risk of anxiety or depression for caregivers, including when the patient's disease is at a more advanced stage, and there is higher symptom burden and poorer physical functioning. Given the high proportion of NENs patients with these issues, the burden on caregivers cannot be underestimated.

General interventions

There is expert consensus on best practice in communication for clinicians caring for patients with cancer [Gilligan]. Patients with NENs may face particular issues with understanding information because of its complexity and the range of investigations and treatments for this group of conditions. Patients will seek information on-line and may find it difficult to discern the quality of the information they access. Health services should compile relevant lists of on-line and/or print resources suitable for patients and family members. The Plain Language Thesaurus for Health Communication can assist health professionals with discussion [CDC resource]. Routine checking for comprehension is best accomplished using the "teach back" technique in which the clinician asks the person to repeat what they have been told "So I can check if I've been clear or if I've left anything out". Given the complexity of this disease, the provision of printed information in "plain English" is also critical. Patients may benefit from the provision of an individualised Treatment and Wellness Care Plan, with template available from https://neuroendocrine.org.au/treatment-wellness-care-plan/.

In addition to these general skills, it is important for health professionals caring for patients with NENs to be curious about the "back story" and develop an understanding of the path to the diagnosis, as this may exert a powerful influence on long-term adjustment. Given this, paying attention to the building of trust early in the relationship, by the use of empathy and careful non-judgmental listening builds a foundation for patient-centred ongoing care.

There is well-established evidence supporting the role of peer support, as an important component of psychosocial care of people affected by cancer, both in the form of support groups [Ussher] and 1:1 telephone support with a matched volunteer [Hoey]. For those isolated due to geographical location, or advanced disease, telephone and online support groups can be an especially effective means of enabling important social connections [Columbus, Street].

There are comprehensive information and support services available via NeuroEndocrine Cancer Australia, and patients affected by NENs should be routinely informed of the availability of these. They include a wide range of patient information, endorsed by a panel of NEN specialists, as well as support services (1:1, face-to-face and online peer support). The organisation also offers a specialist NET Nurse service, available via email (NETNurse@neuroendocrine.org.au) or phone (1300 287 363) on the NeuroEndocrine Cancer Australia website (www.neuroendocrine.org.au/for-patients)

DRAFT

Addressing specific psychosocial issues

i) Fear of recurrence (or progression) (FCR) is defined as “Fear, worry or concern relating to the possibility that cancer will come back or progress” [Lebel]. There is limited data about the prevalence of FCR in NENs patients. One study found clinically significant FCR in 35% of patients who were disease-free after potentially curative pancreatectomy for pancreatic neuroendocrine tumour [Petzel]. Health professionals can ask open questions to determine the level of concern and potential need for referral. Examples include: “Most people with NENs say that they feel anxious and uncertain from time to time. How would you say things are going for you?”; followed with questions about the extent and severity of worry about worsening of their condition and how much this affects their life and relationships. Validation of anxiety is important, however if the person feels that this is affecting their life, they should be offered referral for treatment. FCR does not abate over time and there is strong evidence of the effectiveness of interventions with trained psychologists [Tauber].

ii) Depression and anxiety affect up to 20% of patients with cancer, although this varies depending on the population and cancer type [Mehnert]. There is limited data about the prevalence of mood disorders in patients with NENs. Identification and treatment of depression and anxiety are critical as these conditions undermine the ability of the individual to cope with residual symptoms [Burki], reduce adherence to treatment recommendations [Grenard], and are associated with more than a doubling of readmission rates [Hanrahan].

Patients treated for cancer should be routinely screened for depression and anxiety using a validated measure across a range of time points including when there are changes in disease status and transitions such as completion of a defined treatment protocol [Andersen]. The Distress Thermometer devised by the National Comprehensive Cancer Network (NCCN) may be a useful initial screening tool, as the word “distress” is seen as non-stigmatising. Patients rate their distress on a scale of 0-10 on a linear scale and complete an accompanying problem list. A score of 5 or greater should trigger further questions and assessment [NCCN]. For this purpose, the PHQ-9 which is free to download poses low respondent burden and is quick and easy to score; a score of 10 being the cut-off for moderate depression [Kroenke]. There is compelling evidence of the effectiveness of individual interventions [Faller] and antidepressant medication when required [Cipriani].

Cognitive behaviour therapy (CBT) is an effective treatment for mild to moderate depression. In Australia, a General Practitioner can complete a Mental Health Care Plan which entitles the person up to 10 subsidised sessions with a psychologist. For more severe depression, or when there is insufficient response to CBT**,** antidepressant medication is indicated. In the adult population Selective Serotonin Reuptake Inhibitors are typically first-line because they are safe, moderately well-tolerated and reasonably efficacious [Mahli].

Treatment with antidepressants in any person with a comorbid medical condition should be based on current disease-related symptoms, the side-effect profile of the medication and potential for drug interactions. For patients with NENs, the selection is

DRAFT

complicated by the presence of tumours which may secrete serotonin, histamine, tachykinins and prostaglandins which are associated with abdominal cramps, diarrhoea, flushing and wheezing. A recent systematic review reported on 15 studies of 161 NENs patients who had been treated with serotonin-mediated antidepressants. Of the 72 patients with carcinoid syndrome prior to antidepressant usage, 6 experienced exacerbation and 3 of them chose to cease antidepressants. The remaining 89 patients did not have symptoms of carcinoid before antidepressant use and none developed carcinoid syndrome with antidepressant treatment. [Isenberg-Grzeda]. This is similar to a retrospective review conducted in the US in which <10% of patients developed a combination of flushing, diarrhoea and bloating after initiation of serotonergic medications [Shi]. This data suggests that depression can be treated with an SSRI in patients with NENs. Commencing with a low dose and titrating up whilst monitoring for side-effects allows for early cessation if necessary.

DRAFT

References

1. Wolin EM, Leyden J, Goldstein G, Kolarova T, Hollander R, Warner RRP.Patient-Reported Experience of Diagnosis, Management, and Burden of Neuroendocrine Tumors. Results From a Large Patient Survey in the United States. Pancreas 2017;46:639-647.
2. Vinik, Aaron I. MD, PhD*; Woltering, Eugene A. MD†; Warner, Richard R. P. MD‡; Caplin, Martyn MD§; O'Dorisio, Thomas M. MD‖; Wiseman, Gregory A. MD¶; Coppola, Domenico MD#; Go, Vay Liang W. MD** NANETS Consensus Guidelines for the Diagnosis of Neuroendocrine Tumor, Pancreas: August 2010 - Volume 39 - Issue 6 - p 713-734 doi: 10.1097/MPA.0b013e3181ebaffd
3. Singh, S., Granberg, D., Wolin, E., Warner, R., Sissons, M., Kolarova, T., Goldstein, G., Pavel, M., Öberg, K., & Leyden, J. (2016). Patient-Reported Burden of a Neuroendocrine Tumor (NET) Diagnosis: Results From the First Global Survey of Patients With NETs. *Journal of global oncology*, *3*(1), 43–53. https://doi.org/10.1200/JGO.2015.002980
4. Beaumont JL, Zhimei L, Choi S, et al: Health-related quality of life of patients with neuroendocrine tumor compared to the United States general population. Pancreas 39:271, 2010 (abstr)
5. Leyden J, Pavlakis N, Chan D, Michael M, Clarke S, Khasraw M, Price T. Patient-reported experience of the impact and burden of neuroendocrine tumors: Oceania patient results from a large global survey. Asia-Pacific Journal of Clinical Oncology 2018;14:256-263DOI: 10.1111/ajco.12785
6. Leyden S, Kolarova T, Bouvier C, Caplin M, Conroy S, Davies P, Dureja S, Falconi M, Ferolla P, Fisher G, Goldstein G, Hicks RJ, Lawrence B, Majima Y, Metz DC, O'Toole D, Ruszniewski P, Wiedenmann B, Hollander R, International Neuroendocrine Cancer Alliance (INCA).Unmet needs in the international neuroendocrine tumor (NET) community: Assessment of major gaps from the perspective of patients, patient advocates and NET health care professionals. International Journal of Cancer 2019
7. Gordon LG, Elliott TM, Wakelin K, Leyden S, Leyden J, Michael M, Pavlakis N, Mumford J, Segelov E, Wyld D. The Economic Impact on Australian Patients with Neuroendocrine Tumours. The Patient - Patient-Centered Outcomes Research. https://doi.org/10.1007/s40271-020-00412-z

DRAFT

8. Jacobsen PB, Nipp RD, Ganz PA. Addressing the Survivorship Care Needs of Patients Receiving Extended Cancer Treatment. *Am Soc Clin Oncol Educ Book*. 2017;37:674-683. doi:10.1200/EDBK_175673
9. Girgis A, Lambert S, Johnson C, Waller A, Currow D. Physical, psychosocial, relationship, and economic burden of caring for people with cancer: a review. *J Oncol Pract*. 2013;9(4):197-202. doi:10.1200/JOP.2012.000690
10. Gilligan T, Coyle N, Frankel RMF, Berry DL, Bohlke K, Epstein RM, Finlay E, Jackson VA, Lathan CS, Loprinzi CL, Nguyen LH, Seigel C, Baile WF.Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline. Journal of Clinical Oncology 2017;35:3618-3632
11. Plain Language Thesaurus for Health Communications. Centre for Disease Control and Prevention National Center for Health Marking. https://www.orau.gov/hsc/HealthCommWorks/MessageMappingGuide/resources/CDC%20Plain%20Language%20Thesaurus%20for%20Health%20Communication.pdf (accessed 11.6.2020)
12. Ussher J, Kirsten L, Butow P, Sandoval M. What do cancer support groups provide which other supportive relationships do not? The experience of peer support groups for people with cancer. *Soc Sci Med*. 2006;62(10):2565-2576. doi:10.1016/j.socscimed.2005.10.034
13. Hoey L. Cancer Connect Evaluation Report. Prepared for: Customer Information and Support Service. Centre for Behavioural Research in Cancer, The Cancer Council Victoria: Melbourne, Australia, March 2006.
14. Colombus E, Wakelin K. Clinical Group Work: Embracing Opportunities, Navigating Challenges. In G. Christ, C. Messner & L. Behar (Eds), Handbook of Oncology Social Work. 2014. Oxford University Press
15. Street AF, Wakelin K, Hordern A, Bruce N, Horey D. Dignity and deferral narratives as strategies in facilitated technology-based support groups for people with advanced cancer. Nurs Res Pract. 2012;2012:647836. doi:10.1155/2012/647836
16. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer. 2016;24(8):3265-8
17. Petzel MQB, Parker NH, Valentine AD, Simard S, Nogueras-Gonzalez GM, Kee JE, Pisters PWT, Vauthey J-N, Fleming JB, Katz HG. Fear of Cancer

DRAFT

Recurrence after Curative Pancreatectomy: A Cross-sectional Study in survivors of Pancreatic and Periampullary Tumors. Annals of Surgical Oncology 2012;19:4078-4084

18. Tauber NM, O'Toole MS, Dinkel A, Galica J, Humphris G, Lebel S, Maheu C, Ozakinci G, Prins J, Sharpe L, Smith AB, Thewes B, Simard S, Zachariae R. Effect Of Psychological Intervention on Fear of Cancer Recurrence: A Systematic Review And Meta-Analysis. Journal of Clinical Oncology 2019;37:2899-2915.
19. Mehnert A, et al. Four-Week Prevalence of Mental Disorders in Patients With Cancer Across Major Tumor Entities. Journal of Clinical Oncology 2014;32:3540-3546.
20. Burki TK. Unmet needs of cancer survivors. Lancet Oncol. 2015;16:e106.
21. Grenard JL, et al. Depression and Medication Adherence in the Treatment of Chronic Diseases in the United States: A Meta-Analysis. J Gen Internal Med. 2011;26:1175-82.
22. Hanrahan NP, et al. Examining the impact of comorbid serious mental illness on rehospitalization among medical and surgical inpatients. Gen Hosp Psychiat. 2016;42:36-40.
23. Andersen BL, DeRubeis RJ. Berman BS, Gruman J, Champion VL, Massie MJ, Holland JC, Partridge AH, Bak K, Somerfield MR, Rowland JH. Screening, Assessment, and Care of Anxiety and Depressive Symptoms in Adults With Cancer: An American Society of Clinical Oncology Guideline Adaptation. Journal of Clinical Oncology 2014;32:16-5-1619.
24. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Survivorship Version 1.2019-March 14,2019. NCCN.org
25. Kroenke K, Spitzer R, Williams J. The PHQ-9 validity of a brief depression severity measure. Journal of General Internal Medicine 2001;16;606-613
26. Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R. Effects of Psycho-Oncologic Interventions on Emotional Distress and Quality of Life in Adult Patients With Cancer: Systematic Review and Meta-Analysis. Journal of Clinical Oncology 2013;31:782-793
27. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with

DRAFT

major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357-1366. doi:10.1016/S0140-6736(17)32802-7

28. Malhi GS, Outhred T, Hamilton A, Boyce PM, Bryant R, Fitzgerald PB, Lyndon B, Mulder R, Murray G, Porter RJ, Singh AB, Fritz K. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. Medical Journal of Australia 2018;208:175-180
29. Isenberg-Grzeda E, MacGregor M, Matsoukas K, Chow N, Reidy-Lagunes D, Alici Y. Must antidepressants be avoided in patients with neuroendocrine tumors? Results of a systematic review. Palliative and Supportive Care 2020; 1–7. https://doi.org/10.1017/S147895152000005X
30. Shi DD, Yuppa DP, Dutton T, Brais LK, Minden SL, Braun IM, Kulke MH, Chan JA, Meyer FL. Retrospective Review of Serotonergic Medication Tolerability in Patients With Neuroendocrine Tumors With Biochemically Proven Carcinoid Syndrome. Cancer 2017;123:2735-42

DRAFT