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Prognostic and predictive biomarkers in neuroendocrine tumours

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ABSTRACT

Neuroendocrine tumours are extremely heterogeneous malignancies. Despite marked heterogeneity in clinical course and prognosis, few biomarkers exist to help predict prognosis and guide treatment. Many tumour-based biomarkers (Ki-67, mitotic count, genetic/epigenetic changes and microRNAs) exist, but only Ki-67 and mitotic count have strong evidence to support their routine use. Blood-based markers are easily repeatable, but currently established biomarkers (chromogranin A and urinary 5-HIAA) are difficult to measure accurately in practice. Structural imaging is used routinely via the TNM system. Functional

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imaging such as ^{68}Ga-based and FDG PET may become valuable biomarkers with their increasing availability, aided by ongoing quantitative research. Multiple nomograms have been proposed to integrate the above factors, but most have not been prospectively validated and are difficult to use in practice. Further research should aim to establish robust new biomarkers and integrate existing ones to help optimise NET treatment.

1. Introduction

Neuroendocrine tumours were first described by Oberndorfer in 1907 (Oberndorfer, 1907) due to their potentially malignant character using the name "karzinoide". As they arise from the enterochromaffin cells of the neuroendocrine system, they have more recently been named neuroendocrine tumours. They are most often found in the gastroenteropancreatic (GEP) system (57%) and the lungs (27%) (Yao et al., 2008a,b), and 50% of patients present with metastatic disease (Yao et al., 2008a). Whilst many therapeutic advances have been made in neuroendocrine tumours (NETs) (Lawrence et al., 2011a), 5 year overall survival (OS) for GEPNETs is only 61% (Hallet et al., 2015), and many patients with metastatic disease ultimately succumb to progressive disease.

In contrast to other solid organ tumours, NETs may arise from a wide variety of primary organ sites – the whole gastrointestinal tract (particularly the small bowel), pancreas, and lungs as well as rarer sites such as the thymus and cervix. The primary site of origin appears to also influence prognosis, with colonic, gastric and hepatic NETs having worse overall survival in the metastatic setting (Yao et al., 2008a). Even metastatic NETs from the same primary site are heterogeneous in clinical presentation, aggressiveness and prognosis. For instance, patients with Grade 1 midgut NETs have a median survival of 16.6 years, compared to 1.1 years for Grade 3 NETs (Ahmed et al., 2009). In another study, patients with NET lesions which showed avidity on FDG PET had a median survival of 1.2 years, compared to 10 years for those who did not, indicating the FDG highlights patients with aggressive clinical behaviour and a high proliferative rate (Bahri et al., 2014).

This heterogeneity presents a significant clinical challenge, as patients may either take false comfort from the misconception that NETs are benign when they have aggressive disease, or have an unduly pessimistic outlook when their outcome with a Grade 1 NET is projected to be excellent. Apart from the prognostic implications, heterogeneity also makes it difficult to optimise treatment in NETs. The conduct of clinical trialsis also hampered by the difficulty in selecting a homogenous patient cohort. Recent trials have focussed on specific NET subgroups (such as midgut, pancreatic, or GEPNETs) with potential inclusion of other subgroups (such as lung or hindgut NETs), but this specificity slows patient accrual to trials and makes any findings less generalizable. This clinical need has driven the search for accurate, affordable and repeatable biomarkers to help inform prognosis and predict response to treatment. If identified, these biomarkers would allow administration of the right treatment to the right patient at the appropriate time – avoiding unnecessary side effects from therapy yet administering effective clinical treatment before significant clinical deterioration occurs.

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001), and guidelines exist to guide the conduct and reporting of biomarker studies (McShane and Hayes, 2012; Alonzo, 2005). Several reviews have focussed on blood-based biomarkers in NETs (Modlin et al., 2014; Oberg et al., 2015). Serum-based assays offer advantages in terms of convenience and safety of collection (compared to repeat tissue biopsies). However, older studies have not demonstrated sufficient power to enable accurate prognostication, and have in general looked at individual measures in isolation. Newer studies with multiple analyses show promise, but have not been validated as yet. Molecular imaging has been increasingly employed in guiding management of NETs, with recent studies demonstrating potential prognostic significance. The optimal selection of therapies in a given NET patient at a given point in their clinical course remains an unanswered question. Guidelines (Pavel et al., 2016; Phan et al., 2010) tend to focus on the available evidence in trials conducted to date, based upon the inclusion criteria of those trials. As such, initial anti-proliferative therapy tends to be with somatostatin analogues, with other therapies (such as peptide receptor radionuclide therapy (PRRT), tyrosine kinase inhibitors, or chemotherapy) chosen upon failure of these therapies. The identification of biomarkers that could help predict prognosis and response to individual treatments would allow individual personalization of treatment for each patient to achieve optimal outcomes.

This review was undertaken to evaluate the literature on tissue-based as well as molecular imaging derived biomarkers for neuroendocrine tumours, in order to identify areas where evidence of biomarker utility is robust and where gaps exist so as to direct further research.

2. Tumour-based biomarkers

2.1. Ki-67 index/mitotic count

The Ki-67 index and mitotic count are markers of cell proliferation which have been increasingly utilised and reported since their adoption into the 2010 WHO histological grading system (Klimstra et al., 2010) for NETs of gastroenteropancreatic origin (GEPNETS) (Table 1). It is the most common tissue-based marker used in NETs worldwide.

The mitotic count (MC) has been used as a biomarker for over 20 years. It is conventionally counted over at least 10 high-power fields, and has been shown to have prognostic significance in pancreatic (Pelosi et al., 1996; La Rosa et al., 1996; Hochwald et al., 2002; Ferrone et al., 2007), upper gastrointestinal (Pape et al., 2008a), and bronchial NETS (Beasley, 2000; Travis, 1998; Joseph et al., 2015). It is still used as the primary determinant of grade in bronchial NETs (Travis et al., 2004), along with the presence or absence of necrosis. However, the Ki-67 index often provides additional information which may affect management, particularly in GEPNETs.

Ki-67 plays a very prominent role in NETs compared to other tumours, because of the wide disparity in biological behaviour between different grades of disease. It is present in cells undergoing all parts of the cell division cycle (G1, S, G2 and mitosis) but not in G0 (Scholzen and Gerdes, 2000). Therefore, the percentage cells which are Ki-67 antigen positive (otherwise known as the Ki-67 index, and occasionally shortened to just "Ki-67") reflects the growth fraction of a cell population. Whilst its exact function is still unknown, the