short review

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The NET G3 enigma: dealing with a "new" entity

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Summary Neuroendocrine neoplasms of the gastroenteropancreatic system (GEP-NENs) have historically been graded into well-differentiated neuroendocrine tumors (NETs) G 1 and 2 and undifferentiated neuroendocrine carcinomas (NEC) G3 according to the proliferative index Ki-67, with the latter being larger than 20% for G3 NENs. However, clinical and pathological findings have suggested G3 NENs to be heterogeneous, and the most recent World Health Organization (WHO) classification has further subdivided G3 NENs into NET G3 with differentiated features and a usually lower Ki-67 (20–55%) as opposed to undifferentiated NECs. Currently, however, no standard approach to patients with NET G3 has been defined. As opposed to NET G1/G2, application of somatostatin analogues is not recommended, and the response to platinum-based chemotherapy is inferior when compared to NEC. The objective of this short review is to summarize pathological characteristics as well as therapeutic data obtained in patients with NET G3.

Keywords Neuroendocrine tumor grade 3 · Classification · Chemotherapy · Peptide receptor radiotherapy · Somatostatin analogues

Introduction

Neuroendocrine neoplasms (NENs) are relatively rare, but have been demonstrated to show an increasing incidence worldwide [1, 2]. According to Surveillance, Epidemiology and End Results (SEER) data, the lung is the most common site of origin, followed by the gastrointestinal (GI) tract including the pancreas and the small bowel [3]. Due to peculiar event during embryogenesis, however, neuroendocrine cells can be found scattered throughout the human body giving rise to NENs. Within the GI tract, the majority of NENs are highly differentiated tumors formerly termed carcinoids, which are graded according to the proliferative index as assessed by the Ki-67 index into "NET G1" and "NET G2", while in the lung the term "carcinoid" is still used for G1 and "atypical carcinoid" for G2 tumors [4–6]. A prospective Austrian incidence study has assessed pathological diagnoses of GI-NETs and found an incidence of 2.56/100,000 inhabitants with the majority being found in the stomach [7].

While the features and clinical characteristics of differentiated NETs have been studied in detail in recent decades, more aggressive NENs have only more recently been given more attention. Initially graded as neuroendocrine carcinoma (NEC) if a Ki-67 of more than 20% was documented by immunohistochemistry, these malignancies have historically been treated according to small cell lung cancer. Clinical and pathological data, however, have led to a more refined grading with further distinction between NET G3 and NEC.

In this short overview, recent developments in NET G3 will be summarized and discussed.

Historical development—the Nordic NEC study

The first study to suggest a heterogeneous behavior of—what was then called—NEC/WHO G3 within the GI tract was a retrospective analysis published by Sorbye and coworkers in 2013 [8]. A total of 305 patients (301 with metastatic and 4 with locally advanced, unresectable tumors) were included, and the aggressive nature of the disease was impressively underscored

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by the median overall survival (OS) of 11 months in the 252 patients undergoing chemotherapy and a median OS of 1 month in the 53 patients having only best supportive care. Additional negative prognostic factors identified were elevated LDH, thrombocytosis, impaired performance status and a colorectal origin of the disease. Further analysis, however, disclosed a difference in terms of Ki-67 index, with a cut-off of 55% being suggested to divide between two prognostically different subgroups. While the response rate to platinum-based chemotherapy was significantly lower (15% vs 42%, $p=0.001$), the overall survival was longer in patients with a Ki-67 < 55% (14 months vs 10 months, $p=0.001$).

These data were the first to suggest that platinum-based therapy might not be the optimal therapy for NEN patients with a Ki-67 between 20–55%, while it is still standard therapy for patients with NECs in analogy to pulmonary NECs.

Current classification of NENs

The accumulating clinical and pathological data generated after the Nordic NEC trial are reflected in most current World Health Organization (WHO) classification published in 2017 [5]. One of the major changes (in addition to increasing the Ki-67 cutoff for distinction to between NET G1 und NET G2 to 3%) was the definition of a totally new entity termed NET G3. The distinction between NET G3 and NEC is mostly based on morphology, but as already suggested by Sorbye and coworkers [8], NET G 3 is mostly characterized by a lower Ki-67 index, i.e., between 20–55%, while patients with NEC show a median KI 67 of 80% [5, 9, 10]. Still, the presence of distinct small cell (43%) or large cell (57%) histology defines a NEC even with a lower proliferative index, while NET G 3 patients with higher Ki-67 also exist. In the lung, the proliferative grading is based rather on the mitotic index (>20/HPF) than Ki-67 [6]. NET G3 was initially defined only for pancreatic NENs [5], but has now widely been accepted irrespective of the site of origin [10].

In initial studies on pancreatic NET G3, the underlying "low grade" component as opposed to NEC of the pancreas was thought to be a distinguishing feature, as was the presence of MEN1, DAXX and ATRX mutations [10–14]. Using these criteria, NET G3 of the pancreas were found to have an OS of 99 months as opposed to 17 months for patients with NEC, characterized by small or large cell morphology without a distinguishable low-grade background and a higher rate of TP53 mutations (64% vs 14%).

As compared to differentiated NETs G1 and G2, the high grade NENs (NET G3 and NEC) are still rare, with only up to 15% of NENs being high grade (9% extrapulmonary, 3% within the GI tract).

In terms of molecular characteristics, recent studies have consecutively unraveled the differences between GI-NET G 3 and NECs. In a cohort of 136 patients with GEP-NEN G3, immunohistochemical expression of PD-L1 was assessed and found to be low with only 14 patients (10%) showing immunoreactivity (4 in the tumor cells and 10 with immunoreactive immune cells). In this series, PD-L1 positivity was exclusively found in undifferentiated NEC patients, but not in NENs as far as the presentation of the data allowed extraction of definitive histologies [15]. This underscores another problem when dealing with NET G3 that a lumping with NEC within the same analysis under the basket heading "NEN G3" is still performed without definitive distinction between NEC and NET G3. Tumor mutational burden, however, has also been reported as low for both entities (5.1 for NEC and 6.9 for NET G3), which might explain the unsuccessful attempts to implicate checkpoint inhibitors in the therapy of these patients (for review see [10, 13]). In addition, NET G3 is characterized by a lower MSI rate of around 3% [13, 14].

Treatment of NET G3—the clinicians' dilemma

To date, the optimal first line therapy in patients with NET G3 has not been established, although recommendations in current guidelines have favored treatment approaches based on systemic approaches to pancreatic NETs with the exception of somatostatin analogues (SSA), which is not recommended in any guideline and should be restricted to patients with NET G1/G2 [9, 10].

Following distinction between NET G3 and NEC, however, potential surgical intervention whenever possible is now being advocated in NET G3 patients, and it has been stated that the guidelines for surgery in patients with NET G3 should be similar than for NET G2 [16, 17].

For patients not amenable to surgery, however, no formal prospective trials exist, but the ENETS, the ESMO as well the Nordic guidelines [9, 10, 18] suggest the combination of temozolomide/capecitabine or streptozotocin/5-FU, the mTOR inhibitor everolimus or sunitinib in case of a pancreatic origin as potential first-line therapies.

Limited data on the use of temozolomide-based therapies in NET G3 exist, with one of the largest retrospective analyses having been published by Rogowski and coworkers in 2019 [19]. In this series, 20 patients with NET G3 and 12 with NEC of the GI tract having been treated with temozolomide/capecitabine were analyzed. A progression-free survival (PFS) of 15.3 months with an overall survival (OS) of 22 months was found in this cohort, which was significantly better than the results obtained for NECs (PFS 3.3 and OS 4.6 months, respectively).

The use of everolimus to date is only substantiated by a retrospective analysis of 15 patients with G3 neoplasms with a Ki-67 < 55%, resulting in a median PFS of 6 months, and an OS of 28 months [20]. The authors suggested a higher benefit for patients given the

mTOR inhibitor as first-line therapy, with 3/4 patients having a PFS of 12, 17 and 22 months, respectively.

Sunitinib at a dose of 37.5 mg daily was given to 31 patients with GEP-NEN G3, 26 of whom had tissue available for exact grading [21]. In total, the majority of patients were graded as NECs ($n=20$) and only 6 had NET G3, 4 of whom were rated as responders. Median PFS was 42 days and OS 181 days for the whole cohort, and at the time of analysis 2 patients with NET G3 had died, and median survival could not be calculated. In a retrospective analysis reported by Mizuno at al [22], the effect of sunitinib on 60 pancreatic NETs including 10 with NET G3 was assessed. The authors reported a 1-year PFS of 44%, 40% and 0% for NET G1/G2, NET G3 and NEC, respectively, with 4/10 NET G3 patients rated as PR and suggested a comparable efficacy for sunitinib in NET G3 to NET G1/G2.

These data, however, have to be interpreted with caution, and prospective studies are clearly needed to assess the exact impact of those therapies.

In keeping with prior data, application of cisplatin/etoposide should be reserved for patients with clinically aggressive tumors or a Ki-67 > 55% [9, 10].

While somatostatin-receptor targeting methods are not recommended as the imaging of choice and 18F-FDG-PET/CT is thought to be more sensitive in NEN G3 [10, 23], detection of somatostatin receptors (SSTR2) is still an important information in patients especially with NET G3. Peptide receptor radiotherapy (PRRT) directed against SSTR2 is a highly effective and approved therapy in patients with NET G1/G2 after progression during therapy with an unlabeled SST analogue [24]. No prospective data in NET G3 exist so far, but a recently published retrospective analysis has shown promising results for both NET G3 and NEC [25]. A multicenter analysis including 149 patients with GEP-NEN G3 disclosed 1% complete response, 41% partial remission, 38% stable disease and only 20% progressed during therapy. The median PFS was 14 months with an OS of 29 months. These results are especially promising, as the majority of patients had been pretreated (62 received PRRT as second-line therapy and 57 even later). The subgroup of NET G3 had a better outcome when compared to the undifferentiated patients, with the median PFS being 19 vs 8 months and the OS 31 vs 9 months. When broken down by Ki-67 index, patients with a Ki-67 < 55% ($n=125$) had a longer PFS (16 months) and OS (31 months) when compared to patients with Ki-67 > 55% (PFS 6 months, OS 9 months). While no formal comparison with other forms of therapy has been performed, these results appear superior to other systemic treatments even in the first line. In view of this, assessment of SSTR status preferably by 68-Ga-DOTANOC-PET CT in patients with NET G3 seems reasonable in order select individual patients suitable for PRRT.

Conclusion

The definition of NET G3 has been inevitable since the publication of the Nordic NEC study in 2013 [8], but has left the NET-community—especially clinicians—with more questions than answers. While being apparently more indolent than NEC and less prone to responding to platinum-based therapy, little progress has been made in the therapy of those patients. To date, no standard first-line therapy has been established and the results on which recommendations laid down in the current guidelines are based appear pretty thin. The most promising and solid data, even though retrospective, appear to result from application of PRRT in patients with SSTR-positive tumors. Other than that, the frontline management of patients is dependent on the clinical aggressiveness, i.e. platinum-based therapy and the preference and experience of the respective centers in the use of either chemotherapy as used for pancreatic NET G1/G2 or targeted therapies such as everolimus and sunitinib. Various negatives, however, have been clearly defined including the absence of benefit from checkpoint inhibitors or application of unlabeled SSA. In view of this situation, multinational efforts are clearly needed in the future to advance our knowledge in this field.

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Conflict of interest M. Raderer and B. Kiesewetter declare that they have no competing interests.

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