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Neuroendocrine Cancers (JR Strosberg, Section Editor)

Management of Well-Differentiated High-Grade (G3) Neuroendocrine Tumors

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Opinion statement

In 2017, the World Health Organization (WHO) classification for pancreatic NET was updated to include a new category of well-differentiated high-grade (Ki 67 > 20%) pancreatic tumors (NET G3), distinct from high-grade poorly differentiated neuroendocrine carcinoma (NEC). NET G3 are considered a molecularly, radiologically, and prognostically distinct entity compared to NEC and NET G1/G2. The optimal first-line management in NET G3 and sequencing therapies remains a challenge awaiting future trials taking into consideration the unique characteristics of this category. In this review, we aim to summarize the current evidence in the management of NET G3.

Introduction

Neuroendocrine tumors (NETs) are rare neoplasms that can arise from most organs and characterized by expressing unique diagnostic markers [1]. In addition to the site of origin, NETs are classified pathologically based on morphological features into well-differentiated and poorly differentiated tumors. Furthermore, they are classified by the Ki67 proliferative index and/or the mitotic rate into three grades: low- (grade 1; G1), moderate- (grade 2; G2), and high-grade (grade 3; G3) tumors [2, 3]. This classification has prognostic and therapeutic implications. Well-differentiated NETs tend to have an indolent course with a better overall prognosis than their higher grade counterparts [4–8]. On the other hand, higher grade (Ki 67 > 20%) neuroendocrine neoplasms (NEN G3) carry a less favorable prognosis with a more aggressive disease course. However, multiple reports

have shown substantial heterogeneity within the NEN G3 group. It is increasingly becoming clear that the outcomes of patients with G3 NENs vary greatly and that the tumor grade as assessed by the Ki67 index is insufficient as a stand-alone method to predict outcomes in this group [9•]. The G3 NEN group includes both tumors with well-differentiated and poorly differentiated histology and histological differentiation is emerging as a powerful determinant of survival within the G3 group [10–12].

Therefore, in 2017, the World Health Organization (WHO) classification for pancreatic NET was updated to include a new category of well-differentiated high-grade (Ki 67 > 20%) pancreatic tumor (NET G3) distinct from high-grade poorly differentiated neuroendocrine carcinoma (NEC) [13] (Table 1). It is expected that the forthcoming WHO classification of gastrointestinal malignancies will apply the same grading system to other gastrointestinal NENs.

In this review, we aim to summarize the current evidence in the management of high-grade well-differentiated neuroendocrine tumors (NET G3). The management of poorly differentiated G3 NECs is outside the scope of this review and has been extensively reviewed recently [14, 15••, 16].

Clinical and pathological characteristics of NET G3

NET G3 comprised about 18% of all grade 3 neuroendocrine neoplasms in a recent study [17]. In this study of 204 patients with NEN G3, 37 (18%) had well-differentiated histology compared to 167 (79%) with poorly differentiated morphology. Compared to NEC patients, NET G3 patients were younger, more likely to have functional tumors (14% in NET G3 vs. 2% in NEC), and had primary tumors mostly in the pancreas (65%). In addition, the overall survival for these patients was significantly better than those with NEC (99 months vs. 17 months) but worse than for G1 and G2 NETs [17]. A similar retrospective study of 147 patients with NEN G3 (72 NET G3 and 75 NEC G3) supported the prognostic value of histological differentiation [18]. In this study, the OS of patients with NET G3 was 29 months compared to 20 months in patients with NEC G3. When the non-pancreatic NEN G3 patients were analyzed separately, a greater difference was observed among the groups of NET G3 and NEC G3: 44 months vs. 18 months [18]. Studies limited to G3 NENs of pancreatic origin have yielded similar results showing a markedly worse survival and shorter time

Table 1. 2017 WHO classification of pancreatic neuroendocrine tumors

	Ki 67 index	Mitotic rate
Well-differentiated NENs		
Neuroendocrine tumor (NET) G1	< 3%	< 2/10 HPF
Neuroendocrine tumor (NET) G2	3–20%	2–20/10 HPF
Neuroendocrine tumor (NET) G3	> 20%	> 20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3	> 20%	> 20/10 HPF
Small cell type		
Large cell type		

to recurrence following resection in patients with NEC G3 compared to NET G3 [19]. There seems to be a substantial heterogeneity in regard to survival among the studies done on patients with NEN G3, likely in part due to heterogeneity in the populations studied. It is also increasingly recognized that G1 and G2 NETs can have a component of G3 NEN, either within the primary lower grade tumor or its metastases [20]. Patients with a high-grade G3 component of an otherwise G1/G1 NET have an inferior disease-specific survival (DSS of 55 months) compared to G1/G2 NETs (DSS 162 months) but better than poorly differentiated G3 NECs (DSS 16 months). In this study, patients with G3 NECs were much more likely to have abnormal p53 staining and Rb1 loss or mutation than G1/G2 NETs and G1/G2 NETs with a high-grade component. Also, mutations in DAXX, ATRX, and MEN1 were more likely to occur in G1/G2 NETs (with or without a high-grade component) than in G3 NECs.

Morphologically, NET G3 are well differentiated with Ki67 ranging mostly between 21 and 55% and less commonly above 55. In studies comparing NET G3 to NEC, median Ki67 (range) was 30 (21–70) in NET G3 compared to 80 (25–100) in NEC [2, 17, 18, 21]. In addition, NET G3 are generally positive for synaptophysin and chromogranin (97% and 91%, respectively) [17]. Similar to NEC G3, NET G3 frequently show avidity on 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging which is in contrast to NET G1 and G2 which are frequently without uptake on FDG-PET imaging. In a study of 86 patients with NEN G3 assessed by FDG-PET, 9/12 (75%) of NET G3 had positive FDG-PET compared to 56/64 (88%) in NEC patients indicating that both tumor groups have high metabolic activity [17]. FDG-PET is therefore unable to discriminate between NET G3 and NEC G3. On the other hand, most NET G3 patients (87–92%) have a positive somatostatin receptor imaging (SRI) compared to less than half that frequency in NEC patients [17, 22]. Furthermore, NET G3 has distinct molecular profile compared to NEC; for example, loss of expression of *DAXX* and *ATRX* is seen in well-differentiated pancreatic NET G3 compared to *Rb1*, *KRAS*, and *P53* mutations in poorly differentiated tumors [10, 23–26]. The diagnosis of the subgroups of G3 NENs (NECs and NETs) can be challenging, even for expert pathologists [27]. The distinction between G3 NETs and G3 NEC may be aided by immunohistochemical staining for somatostatin receptor type 2A (SSTR2A), p53, and Rb1 [26]. In a study of G3 NENs, abnormal staining patterns of p53 and Rb1 were seen in the majority of poorly differentiated NECs, usually in the absence of SSTR2A positivity while staining patterns remained normal in well-differentiated G3 NETs with most of the tumors expressing SSTR2A. Recently, morphologic criteria were proposed as a way to distinguish between G3 NECs and G3 NETs [28]. Organoid growth pattern, capillary network in direct contact with tumor cells, and absence of desmoplastic stroma were suggestive of G3 NETs but these criteria need to be further validated before being adopted for clinical use.

Treatment

Over the years, NET G3 patients have been treated similar to NEC given the previous classification and the lack of recognition that these are

clinically very different malignancies. Many of the treatment paradigms were extrapolated from the small cell lung cancer data with platinum-based therapy widely recommended in the frontline setting [17, 21, 29]. However, multiple retrospective studies have suggested that NET G3 may be relatively resistant to the effect of platinum-based cytotoxic therapy. As these tumors are well-differentiated, they probably should be treated and evaluated as "aggressive version" of NET G2 rather than managing them as poorly differentiated NEC. Furthermore, emerging data suggest that small cell carcinoma of pulmonary primary is a genetically different malignancy from extrapulmonary small cell carcinoma and extrapulmonary non-small cell NEC [30].

Platinum-based therapy

The optimal first-line therapy for NET G3 is unclear given the recent recognition of this subgroup and lack of prospective trials dedicated to this group. In general, while first-line treatment for G3 NEC had been mainly with platinum-based chemotherapy, multiple retrospective cohorts suggest a low response to platinum-based therapy in NET G3 patients ranging from 0 to 17% [17, 21, 29] (Table 2). The NORDIC study included 252 patients with NEN G3 from GEP origin [21]. Treatment outcomes with platinum-based regimens were significantly worse for those with Ki 67 index < 55% compared to those > 55% (response rate of 15% vs. 42%, respectively). However, the study did not provide responses to chemotherapy based on the histological differentiation of the tumors, and some of those responses seen in the Ki 67< 55% group could have been driven by poorly differentiated tumors [21]. In a multicentric study of 37 patients with NET G3 in Europe, 12 patients were treated with platinum-etoposide first-line chemotherapy with objective response rate (ORR) only seen in 2 (17%) patients compared to 39/113 (35%) in the NEC cohort [17]. Median progression-free survival (PFS) was only 2.4 months in NET G3 compared to 5 months in the NEC cohort (P = 0.03) [17]. Similarly, in a single-center retrospective study in the USA, only 1/10 (10%) of NET G3 patients had ORR to platinum agents compared to 37% in NEC [22]. These low responses were further confirmed in two additional studies [31, 29]. Hijioka et al. reported a study of 70 patients with pancreatic NEN G3 in which 70% had NEC and 30% had NET G3 [31]. None of the patients with pancreatic NET G3 had a response to platinum-based therapy. On the other hand, most patients with NEC responded to platinum-based chemotherapy 19/31 (61.3%). Furthermore, the investigators in the same study found that Rb loss and *KRAS* mutations, which are more likely to be found in NEC compared to NET G3 (54.5% vs. 0% and 48.7% vs. 0%, respectively), are predictive of response to platinum-based chemotherapy even in NEC-G3 [31] (Table 2).

The activity of 5-fluorouracil and oxaliplatin (FOLFOX) regimen has been previously investigated in high-grade NEC patients with reasonable responses but short PFS [32]. In a retrospective study of 17 patients with NEC mainly of GEP and pulmonary primaries, 5 patients had PR with no CR (ORR 29%). mPFS was only 4.5 months and OS was 9.9 months

Table 2. Selected studies evaluating different therapeutic agents in the management of NET G3

	Tumor characteristics	Number of patients	Study type	Ki67 for G3 NET; median (range)	Therapy used	ORR for NET G3	OS (months)	PFS (months)
Heetfield 2015	NEN G3; GEP	NEN G3: 12 G3 NET and 113 NEC	Retrospective; multicenter	31 (21–70)	Platinum/etoposide	17% in G3 NET vs. 35% in NEC	Not reached	2.4
Vélayoudom-Céphise 2013	Non-small cell thoracic and GEP G3 NEN (including G3 NET)	10 (4 G3 NET; 16 NEC)	Retrospective; single-center	21 (21–60)	Cisplatin/etoposide	0%	41	NR
Sorbye 2013	G3 NEN with Ki67 > 20%; GEP	252 (136 with Ki67 < 55%; 154 with Ki67 ≥ 55%)	Retrospective; multicenter	NR	Cisplatin/etoposide; Carboplatin/etoposide; Carboplatin/etoposide/vincristine	15% for Ki67 < 55 (vs. 42%)	For Ki67 < 55% was 14 months	NR
Raj 2017	Pancreatic NEN with Ki67 > 20%	NEN G3: 16 NET G3 and 29 NEC	Retrospective; single-center	47 (25–80)	Platinum/etoposide or platinum/oxaliplatin	1/10 (10%)	NR	NR
					Alkylating agents (temozolomide or decarbazine-based therapy)	6/12 (50%)	NR	NR
Hijioka 2017	Pancreatic NEN G3	NEN G3: 21 NET G3 and 49 NEC	Retrospective; multicenter	28.5% (15–53)	Platinium-based	0/8 (0%) in NET G3	41.8	
					Everolimus	0% (0/3)		
					Gemcitabine-based	0/3		
					Fluoropyrimidine	0/2		
Sahu 2019	GEP, Lung and unknown intermediate–high-grade NET	TOTAL of 32: 21 grade 2 and 11 grade 3	Retrospective; single-center	NR	CAPTEM	Not clear for NET G3: For overall, ORR 46.9%	NR	NR
Rogowski 2019	NEN G3	Total of 32 patients	Retrospective; multicenter		CAPTEM	DCR 70% in NET G3 and 30% NEC	22	15.3
Apostolidis 2018	NET G3; pancreatic	89 patients	Retrospective; single-center	NR	Platinum/etoposide	38.2% (DCR 70.6%)	NR	6.7
					FOLFOX	64.7% (82.4%)	NR	8.6
					Temozolomide	12% (58.3%)	NR	10.8
Panzuto 2017	NET G3; pancreatic	15 patients	Retrospective; multicenter	30% (22–55)	Everolimus	NR	28	6
Pellat 2017	NEN GEP	31 patients: 6 with NET G3	Phase II prospective, single-arm	NR	Sunitinib	ORR was 12.9% for NEN G3	181 days	42 days
Mizuno 2018	NEN; pancreatic	60 total: 10 with NET G3	Retrospective; single-center	NR	Sunitinib	60%	NR	NR
Thang 2018	NEN G3							

Table 2. (Continued)

	Tumor characteristics	Number of patients	Study type	Ki67 for G3 NET; median (range)	Therapy used	ORR for NET G3	OS (months)	PFS (months)
		28 total (22 with Ki67 < 55%; 6 with Ki67 ≥ 55%)	Retrospective; single-center	For Ki67 ≤ 55% group: median Ki 67 28%	PRRT (177Lutetium, 90Yttrium)	ORR 35% (7/20) in NET G3	46 Ki67 ≤ 55%	mPFS 12 months Ki67 ≤ 55% group; mPFS 4 months Ki67 > 55% group
Carlsen 2019	NEN G3; GEP	58 with NET G3	Retrospective; multicenter	NR	PRRT (177Lutetium, 90Yttrium or 111Indium)	ORR 42% and 51% SD	44 months	19 months
Patel 2019	NEN G3	18 with NET G3	Phase II prospective, single-arm	NR	Nivolumab+ipilimumab	44%	NR	NR

[32]. Similarly, the evidence of activity in NET G3 is also scarce. In a European retrospective study of 89 patients with NET G3, 17 patients were treated with FOLFOX with 64.7% response rate [14] (Table 2).

Overall, these tumors seem to be less responsive than NEC G3 to platinum-based therapy which argues against using these regimens, at least as first-line in these patients.

Temozolomide

The activity of the alkylating agent, temozolomide, has been established in metastatic well-differentiated grade2/3 pancreatic NET in multiple studies [33–35]. Most recently, a randomized phase II trial (ECOG-ACRIN 2211) reported the activity of temozolomide combined with capecitabine compared to temozolomide monotherapy in 144 patients with grade 1/2 well-differentiated pancreatic NET [36]. ORR was 28% in the monotherapy arm compared to 33% in the combination arm. There was more than 8 months improvement in PFS in the combination arm compared to the monotherapy arm (mPFS 22.7 vs. 14.4 months, respectively; HR = 0.58; p = 0.023). This PFS benefit translated into an OS benefit with HR of 0.41 (mOS 28 months vs. not reached in the monotherapy and combination arm, respectively; p = 0.012) [36]. Similarly, multiple studies have suggested the efficacy of temozolomide-based therapy in patients with NET G3 [22, 37] A retrospective study from Australia reported the efficacy of CAPTEM (capecitabine and temozolomide) in patients with metastatic well-differentiated intermediate or high-grade (grade 3) NETs [37]. All included patients (32) were ineligible for PRRT and had FDG-avid disease on PET scan. Twenty-one (66%) patients had grade 2 disease and 11 (34%) had grade 3 disease. ORR was 46.9% in the overall population with 15.6% of patients having stable disease. The study did not give detailed information on responses based on NET G3 compared to other tumor groups [37]. The activity of CAPTEM was recently delineated in a retrospective study of patients with NEN G3 from 4 Polish clinical centers [38]. Thirty-two patients with NEN G3 were treated with CAPTEM with disease-control rate being significantly higher in the NET G3 group compared to NEC (70% vs. 30%). Additionally, PFS was significantly higher in the NET G3 group with median PFS of 15.3 months vs. 3.3 months in the NEC group. Similarly, median OS was 22 months compared to 4.6 months, respectively [38]. A larger European retrospective study of patients with NET G3 included 89 patients with primary tumor mainly in the pancreas [14]. Patients received different first-line palliative chemotherapy regimens: platinum-etoposide (EP) 34, FOLFOX 17, temozolomide 12, and others. ORR was noted to be 38.2% for EP, 64.7% for FOLFOX, and 12% for temozolomide monotherapy. Compared to EP, the other treatment groups showed a trend towards a prolonged PFS (FOLFOX 8.6 months, p = 0.151 and TEM 10.8 months, p = 0.333) [14]. A recent retrospective multicenter study evaluated the activity of temozolomide-based therapy in patients with G3 NENs [39]. In this study, the time to treatment failure (TTF) in patients with well-differentiated G3 NETs was 5.8 months. Overall survival and objective response rate for the same group was 30.1 months and 52%, respectively.

The currently open clinical trial (ECOG-ACRIN EA2142) will better help to assess the activity of CAPTEM in a prospective fashion. This trial is a randomized phase II trial comparing CAPTEM to platinum and etoposide combination in patients with advanced GEP-NEN G3 excluding small cell histology (NCT02595424).

Somatostatin analogs (SSAs)

Given the high frequency of somatostatin receptor expression of NET G3 as confirmed with either receptor PET imaging or immunohistochemical staining, therapy with somatostatin analogs is reasonable. No prospective trials have been performed but there is substantial anecdotal evidence to suggest there is a benefit. Progression-free survival is expected to be shorter in G3 NETs than in G1/G2 NETs. For patients with somatostatin receptor positive G3 NETs, a trial of somatostatin analogs is reasonable but it is recommended that imaging be performed every 2–3 months to assess for progressive disease and to allow a change to a different regimen if progression is noted.

Everolimus

The activity of everolimus in NET G1/G2 is well established with the RADIANT trials showing improvement in PFS and leading to US FDA approval for patents with well-differentiated NET of gastrointestinal or lung origin [14, 40–43]. Few case reports and a recent retrospective study from Italy showed possible activity of everolimus in patients with pancreatic NET G3 [44–47]. The study was done in Italy and only included patients with advanced NET G3 with well or moderately differentiated histology and Ki 67 ≤ 55%. Fifteen patients were included. Median PFS was 6 months and OS was 28 months [47].

Sunitinib

Sunitinib, a tyrosine kinase inhibitor with anti-angiogenesis characteristics, has been shown to be effective in well-differentiated pancreatic NET [48]. The activity has been shown in a randomized, double-blind, placebo-controlled, phase III study of sunitinib in patients with advanced well-differentiated pancreatic NET with improvement of median PFS from 5.8 in placebo arm to 12.6 months in the sunitinib arm [49]. These results led to the US FDA approval of sunitinib in patients with well-differentiated advanced pancreatic NET. Similar activity seems to exist in NET G3. In an open-label phase II, non-randomized prospective trial, 31 patients with GEP-NEN G3 were given sunitinib at a dose of 37.5 mg/day as continuous daily dosing until progression or unacceptable toxicity [50]. Twenty-seven patients (88%) had received prior chemotherapy with two patients receiving 5 different lines of chemotherapy. Among 31 patients evaluated for response, 4 (12.9%) patients had ORR; DCR was 58%. There was no correlation between tumor differentiation and response to therapy. However, only 6 patients with NET G3 were included in this study [50].

In a Japanese retrospective study of 60 patients with pancreatic NEN, sunitinib was administered at initial dose of 18.75 mg daily with dose-escalation in the absence of grade ≥ 2 (max dose 37.5 mg) [51]. For the overall population, ORR was 33.3% with 48.3% stable disease. In the 10 patients with NET G3, ORR was 60% (6/10 PR) and 30% SD (3/10). None of the NEC patients had any response to sunitinib. Interestingly, PFS was not different between NET G1/G2 and NET G3 ($p = 0.975$). In contrast, NEC G3 patients had significantly worse PFS compared to NET G1/G2 ($p < 0.001$) and NET G3 ($p = 0.005$) patients. In a multivariate analysis of factors affecting PFS from the start of sunitinib administration in the same study, poor differentiation was the only significant factor [51].

PRRT for G3 NET

Peptide receptor radionuclide therapy (PRRT) has shown promising activity in patients with well-differentiated NETs that express somatostatin receptors [52]. Most recently, the NETTER-1 trial (phase III study) showed OS benefit in patients with well-differentiated NET randomized to ^{177}Lu-Dotatate compared to higher dose of long-acting octreotide[52] ORR was 18% in ^{177}Lu-Dotatate group versus 3% in the control group ($p < 0.001$). This study led to the FDA approval of lutetium ^{177}Lu-Dotatate for somatostatin-positive GEP-NETs. The study did not include NET G3 as it only included patients with well-differentiated histologic features defined as Ki67 index of 20% or less.

NET G3 display unique features with not only their FDG-PET avidity but also somatostatin receptor expression (87–92% positive on SRI) [17, 22]. These features make PRRT a potential relevant therapeutic option in these patients [53••, 54–56] A retrospective study on the use of PRRT in patients with NEN G3 in Australia was recently reported [55]. Twenty-eight patients with NEN G3 (6 with Ki 67 > 55% and 22 with Ki67 ≤ 55%) were treated with lutetium (^{177}Lu)-based PRRT. Treatments were given with sensitizing chemotherapy (fluoropyrimidine or CAPTEM). In total, DCR was 61% with 57% PR and 4% SD based on SSTR imaging 3 months after last PRRT cycle (Table 2). When assessing response by computerized tomography, DCR was 74% with 35% ORR. Median PFS was 9 months for the overall population, 12 months for Ki 67 ≤ 55%, and 4 months for Ki67 > 55% group. In addition, mOS was 46 months and 7 months for Ki 67 ≤ 55% and Ki 67 > 55% groups, respectively. Similar to the aforementioned study, a recent metacentric European study reported the experience with PRRT for NEN G3 over the last two decades in 149 patients (GEP 83%; unknown primary 17%) [53••]. Fifty-eight (39%) were classified as NET G3. Most patients (80%) in the study received prior medical treatments (50% somatostatin analog and 59% chemotherapy). As in the previous study, the results were promising with ORR reaching 42% and DCR of 93% in NET G3. Interestingly, comparable efficacy was also seen in the NEC group but with worse survival outcomes. Median PFS and OS were 19 and 44 months, respectively, for NET G3. Grade 3/4 adverse events were seen in 13% of patients, most frequently hematological and renal toxicities [53••]. These results show the promising activity of PRRT

in NET G3 patients. Ideally, the efficacy of PRRT in patients with NET G3 should be evaluated in clinical trials, perhaps compared to temozolomide-based therapy, but given the relative rarity of this disease entity, accrual to such a trial will likely be challenging. For the time being, PRRT can be considered as a choice for patients with somatostatin expressing G3 NETs, especially upon progression on somatostatin analog therapy, but the optimal sequencing in regard to other treatment options is not known.

Immune checkpoint inhibitors

Programmed death ligand 1 (PD-L1) and PD-1 inhibitors have shown activity as monotherapy in Merkel cell carcinoma [57, 58] and in combination with chemotherapy in the first-line setting in extensive-stage small cell lung cancer [59]. Multiple trials are currently investigating the activity of such agents in NET patients. Most recently, the KEYNOTE-158 study (phase II) reported the results of pembrolizumab in a cohort of 107 patients with well- and moderately differentiated NET [60]. Pembrolizumab showed limited activity with ORR being only 3.7%, mPFS of 4.1 months, and mOS not reached. It was not clear whether KEYNOTE-158 included NET G3 patients. The limited activity seen in KEYNOTE-158 could be partially explained by the overall low tumor mutation burden in well-differentiated pancreatic NET, even when compared to pancreatic adenocarcinoma [61]. In contrast, NEN G3 have higher mutational burden, making them potential target for immune checkpoint inhibitors [62–65]. Pembrolizumab was studied in a small study of patients with NEN G3 previously treated with platinum-containing chemotherapy. The overall response rates were disappointingly low at 5% but the details of the patient cohort composition, most importantly differentiation, were not reported [66]. Another trial evaluated the efficacy of spartalizumab, a monoclonal anti-PD-1 antibody, in multiple small cohorts of patients with NENs including a cohort of poorly differentiated NEC G3 [67]. Responses were uncommon and it is unlikely that this drug will have significant single-agent activity. Most recently, the DART basket trial reported promising activity of combination immunotherapy with ipilimumab (1 mg/kg every 6 weeks) and nivolumab (240 mg every 2 weeks) in patients with NEN G3. Fifty-six percent of patients (18/32) were with NEN G3 of non-pancreatic origin. ORR was 44% in NEN G3 compared to no ORR seen in low/intermediate NET [68]. The sub-classification of the NEN G3 patients (NET G3 vs. NEC) was not provided in the DART trial. The role of immunotherapy in high-grade NENs remains to be elucidated.

Although the prevalence of microsatellite instability (MSI) appears to be very low, testing for MSI is reasonable given the US Food and Drug Administration (FDA) tissue-agnostic indication for the use of nivolumab or pembrolizumab in patients with MSI-high malignancies regardless of origin.

Surgery

Very little is known about the role of regional therapy such as surgery, radiation, ablative therapy, and embolotherapy in patients with G3 NETs. Until more data become available, the locoregional approach should follow the treatment paradigms for NET G2 [69]. A recent retrospective study of patients with G3

NENs (mostly G3 NECs) suggested a survival benefit in following resection in patients undergoing intended curative resection and/or ablation, especially in those with tumors with a Ki 67 proliferative index less than 55% [70]. Additional small studies have indicated a potential survival benefit in patients undergoing aggressive locoregional therapy [71, 72] but as with other similar studies, there is a high chance of selection bias influencing the results. For patients with clearly resectable NET G3 primary tumors and metastases, a thorough multidisciplinary evaluation is recommended followed by consideration of resection. The benefits of an incomplete debulking remain unknown and if such therapy is considered, patients should be considered for systemic therapy for several months prior to attempted resection to observe the clinical behavior of the malignancy. Such patients showing rapid progression with emergence of new metastatic lesions are unlikely to benefit from aggressive locoregional therapy but patients with stable disease or minimal progression can be considered for such therapy, ideally after multidisciplinary evaluation.

Conclusions

NET G3 is considered a molecularly, radiologically, and prognostically distinct entity compared to NEC and NET G1/G2. While patients with NET G3 have been treated mainly with platinum-based agents over the years, there is growing evidence that such agents may not be very effective in NET-G3 with reported ORR of 0–17%. As delineated in this paper, most of the current evidence derives from retrospective cohorts subject to significant inherent bias and only few small single-arm prospective studies exist. Therefore, the optimal sequence of treatments for NET G3 remains unknown. Overall, after confirming the diagnosis of

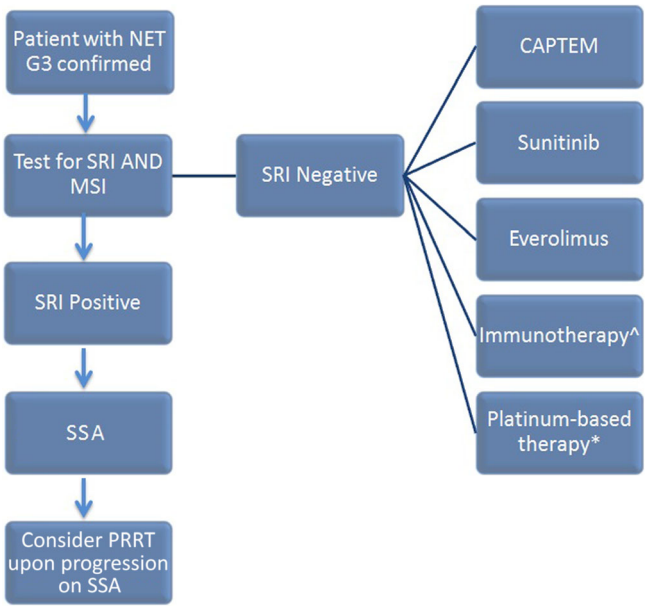

Fig. 1. Suggested treatment algorithm for well-differentiated grade 3 neuroendocrine tumor (NET G3) patients. ^ Especially if MSI-high. *Can be considered for Ki 67 > 55 or when poorly differentiated component is detected/suspected. SRI, somatostatin receptor imaging; MSI, Microsatellite instability; SSA, Somatostatin analog; CAPTEM, Capecitabine and temozolomide.

NET G3 by experienced pathologist, testing with somatostatin receptor imaging, such as with gallium 68 PET/CT, is reasonable (Fig. 1). Carefully selected patients with resectable liver metastases should be considered for aggressive locoregional therapy consisting of surgery with or without ablative therapy. For patients with advanced disease positive on SRI, upfront therapy with SSAs is reasonable with close monitoring for progression. At the time of progression, a referral for PRRT can be considered given the excellent responses and PFS/OS seen with this therapy and limited toxicity. An advantage of earlier PRRT (prior to other chemotherapeutic agents) is that there is less potential for bone marrow toxicity compared to post-chemotherapy PRRT. When PRRT is unavailable, or when patients progress after PRRT, testing for microsatellite instability (MSI) is reasonable given the US FDA tissue-agnostic indication for the use of nivolumab or pembrolizumab in patients with MSI-high malignancies regardless of origin. Indeed, further data is needed to assess whether the activity of the combination of nivolumab and ipilimumab seen in the DART trial is reproducible and whether it was mainly driven by the NEC or NET G3 component. As platinum-based therapy has limited activity in NET G3, temozolomide-based therapy (such as CAPTEM) is reasonable option, especially in patients with pancreatic primary and/or in patients with NET G3 showing a more aggressive clinical behavior. Other regimens, such as sunitinib, everolimus, or cytotoxic chemotherapy such as FOLFOX or FOLFIRI, can be considered. Indeed, other platinum-based regimens can also be considered, especially when Ki67 > 55% or when poorly differentiated component is detected or if the disease course is more aggressive. Future trials are certainly needed with special attention to the heterogeneity of NEN G3 and the unique characteristics of NET G3 in its prognosis and response to therapy compared to NEC.

Compliance with Ethical Standards

Conflict of Interest

Mohamad Bassam Sonbol declares that he has no conflict of interest. Thorvardur R. Halfdanarson has received research funding from Ipsen and has served on advisory boards for Curium and Lexicon Pharmaceuticals. Research funding from Thermo Fisher Scientific

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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