Treatment Landscape of Advanced High-Grade Neuroendocrine Neoplasms

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Abstract: Grade 3 neuroendocrine neoplasms (NEN G3) are high-grade (Ki-67 index >20%) neuroendocrine malignancies that comprise both rapidly proliferating, well-differentiated neuroendocrine tumors (NET G3) and poorly differentiated neuroendocrine carcinomas (NEC). The phenotypic differences between NET G3 and NEC stem from differences in their underlying genomic alterations. As a result of these differences, NET G3 is molecularly, radiologically, and prognostically distinct from NEC. The optimal management of NET G3 and NEC is currently being refined through clinical trials that focus on NET G3 and NEC as separate entities. This review aims to summarize the current understanding of NEN G3 by distinguishing between NET G3 and NEC and describing the clinical implications associated with each.

Introduction

Neuroendocrine neoplasms (NEN) arise from the abundant system of neuroendocrine cells within the human body. These cells are typically found in the epithelium of various organs, including the gastrointestinal tract, pancreas, and lungs.[1] Up to 25% of NEN are functional and release distinctive hormones into the bloodstream, including amines, polypeptides, and prostaglandins.[2-4] NEN are pathologically classified according to their site of origin, morphologic features, grade, and differentiation.[5-7] Within this system, they are morphologically subclassified as well differentiated or poorly differentiated.[6] In addition, the grade is based on the Ki-67 proliferative index and/or mitotic rate. The grade may be low (G1 with Ki-67 <3%), moderate (G2 with Ki-67 3%-20%), or high (G3 with Ki-67 >20%).[5,6] Currently, the term *neuroendocrine tumor* (NET) refers to a well-differentiated neoplasm (G1-G3), whereas *neuroendocrine carcinoma* (NEC) indicates a poorly differentiated

Table 1. World Health Organization Classification and Grading Criteria for Neuroendocrine Neoplasms, 2019

Type	Differentiation	Ki-67 Index, %	Grade	Mitotic Rate, mm²
Neuroendocrine tumor, G1	Well differentiated	<3	Low	<2
Neuroendocrine tumor, G2	Well differentiated	3-20	Intermediate	2-20
Neuroendocrine tumor, G3	Well differentiated	>20	High	>20
Neuroendocrine carcinoma, small cell type	Poorly differentiated	>20	High	>20
Neuroendocrine carcinoma, large cell type	Poorly differentiated	>20	High	>20
Mixed neuroendocrine/non-neuroendocrine neoplasm	Well or poorly differentiated	Varies	Varies	Varies

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carcinoma.[6,8-10] Therefore, the term *NEN G3* covers all high-grade neuroendocrine malignancies with a Ki-67 index higher than 20%: NET G3 if well differentiated and NEC if poorly differentiated (Table 1).[8,9,11] This rigorous classification system makes possible a more informed prognosis and superior therapeutic decision making.[8,12-14] This review focuses on the advanced/metastatic NEN G3 group, which are heterogeneous in terms of differentiation, grade, management, and outcomes.

Clinical Characteristics

Grade 3 Neuroendocrine Tumor

NET G3 is a recently recognized entity that makes up approximately 18% of all NEN G3.[3] When compared with patients who have NEC, those with NET G3 are younger and more likely to have functional tumors (14% with NET G3 vs 2% with NEC).[3] The most common primary organ of an NET G3 is the pancreas (65%).[3] Morphologically, NET G3 is well differentiated, with the Ki-67 index ranging mostly between 21% and 55% and less commonly above 55%.[3,5,9,15,16] The median Ki-67 indices in studies comparing NET G3 with NEC were 30% (21%-70%) and 80% (25%-100%), respectively.[3,5,9,15,16] NET G3 generally stains positive for synaptophysin and chromogranin (97% and 91%, respectively), but other markers, including insulinoma-associated protein 1 (INSM1), are increasingly being used and may be particularly valuable in NEN G3.[3,17] Additionally, it has been shown that NET G3 stains positive for somatostatin receptor type 2A (SSTR2A) by immunohistochemistry, whereas NEC tends to have abnormal nuclear p53 and Rb1 staining. Furthermore, NET G3 has a distinct molecular profile in comparison with NEC.[18,19] Mutations in *MEN1*, *DAXX,* and *ATRX* are seen in well-differentiated pancreatic NET G3, whereas *RB1*, *KRAS*, and *TP53* mutations are commonly found in poorly differentiated NEC.[9,18,20,21]

NET G3 often shows avidity for ^{18}F-fluorodeoxyglucose (^{18}F-FDG) on positron emission tomography (PET), whereas NET G1 and G2 frequently do not.[3] In a study of 86 patients with NEN G3, 9 of 12 patients (75%) with NET G3 had ^{18}F-FDG avidity on PET vs 56 of 64 patients with NEC (88%), suggesting that both tumor types have a high rate of metabolic activity [3] Other investigators have also reported that most NET G3 have hypermetabolic uptake, but the avidity may not be homogeneous.[22,23] As a result, ^{18}F-FDG PET is unable to differentiate between NET G3 and NEC.[3,4,14] On the other hand, somatostatin receptor positivity is seen on imaging in most patients with NET G3 (87%-92%) but in fewer than half of those with NEC.[3,4,24]

Lastly, heterogeneity regarding survival seems to be substantial among the studies evaluating NEN G3. This difference is in part due to the heterogeneity of the populations studied. Currently, subgroups are better recognized, and the identification of mixed tumors of different grades is being acknowledged. As would be expected, the rate of disease-specific survival is lower in patients with a high-grade G3 component than in patients who have NET G1 or G2.[19]

Neuroendocrine Carcinoma

NEC, which is poorly differentiated by definition, accounts for 5% to 10% of NEN.[25] Although the current 2019 World Health Organization classification of NEN categorizes NEC as either small cell or large cell,[26] the truth is that many patients have NEC that cannot confidently be categorized as one variant or the other. Small cell carcinoma is most prevalent in the lung and is strongly related to smoking, which explains why much of the scientific literature concerns this entity.[27] NEC typically stains positive with synaptophysin but negative with chromogranin; however, INSM1 is increasingly being used as a marker of neuroendocrine differentiation.[8,14,28] NEC also tend to demonstrate abnormal staining of p53 and Rb1, and SSTR2A staining is absent.[18,20,21,29]

Both NEC and NET G3 are classically positive on ^{18}F-FDG PET imaging; therefore, no significant difference is seen between the 2 diseases.[13,30] The maximum standard uptake value on ^{18}F-FDG PET may predict outcomes of NEC, but further studies are needed to confirm these findings.[30] The relevance of somatostatin receptor imaging in patients with NEC is uncertain, but results on somatostatin receptor imaging tend to be negative in the vast majority of cases.[31]

NEC has a poor prognosis in general, but high-quality data are lacking. In a retrospective study from the Netherlands, 1544 cases of extrapulmonary NEC were evaluated. This study demonstrated an overall 5-year relative survival rate of 38% among patients with local/regional disease (n=447) and 7% among those with extensive disease (n=582).[32] Dasari and colleagues demonstrated a significant difference in survival of patients with NEC according to the morphologic subtype (P<.001).[7] Overall, small cell histology was associated with worse median and 5-year survival at most primary sites.[7]

Therapies for NET G3

Platinum-Based Therapies

For patients with unresectable or advanced NET G3, the optimal first-line therapy is unclear, given the paucity of prospective trials. The NORDIC study included 252 patients with NEN G3 of gastroenteropancreatic (GEP) origin, but histologic differentiation was not disclosed. Response rates with platinum-based regimens were significantly lower for those with a Ki-67 index lower than 55% than for those with a Ki-67 index higher than 55% (15% vs 42%, respectively). However, the overall prognosis for those with a Ki-67 index higher than 55% was significantly worse.[16] A subsequent report from the NORDIC study after morphologic re-evaluation found that progression-free survival (PFS) was similar among patients with NET G3 and those with NEC, at 5 months, but overall survival was significantly longer in the patients with NET G3 than in those with NEC, at 33 vs 12 months, respectively.[33] A European multicentric study of 37 patients with NET G3 used platinum/etoposide in first-line therapy for 12 patients with NET. The objective response rate (ORR) was 17% (2/12) in the patients with NET G3 vs 35% (39/113) in the NEC cohort. The median PFS (mPFS) was 2.4 months in the NET G3 cohort vs 5 months in the NEC cohort (P=.03).[3] These low ORRs were further confirmed by multiple other studies, including a study by Hijioka and colleagues in which not a single response to platinum-based therapies occurred in the patients with pancreatic NET G3.[2,4,18] On the other hand, a more recent retrospective study from China looking at platinum/etoposide revealed no significant difference between mPFS in patients with NET G3 and those with NEC (2.6 vs 3.6 months; P=.318) and response rates of 30% and 25%, respectively. Results were similar in a recent multicenter retrospective analysis evaluating patients with NET G3 who received platinum/etoposide in a first-line setting (n=34): an ORR of 35.3%, a disease control rate (DCR) of 67.6%, and mPFS of 5.2 months.[12] Additionally, in a study conducted at Mayo Clinic, the response rate (25%) and mPFS (2.94 months) were comparable with those observed in more recent studies of platinum/etoposide for NET G3.[34] Given these conflicting results, platinum/etoposide is probably not the preferred option for patients with NET G3 but can be considered when the Ki-67 index is higher than 55% or in cases of rapid clinical progression.

The combination of leucovorin, oxaliplatin, and 5-fluorouracil (5-FU; FOLFOX) has also been evaluated in NET G3. In a European retrospective study of 89 patients with NET G3 in which 17 patients were treated with FOLFOX, the response rate was 64.7%.[35] Another retrospective analysis done in multiple institutions evaluated 36 patients with NET G3 who received FOLFOX in the first-line setting; the outcomes of ORR, DCR, and mPFS were 52.8%, 80.6% and 6.0 months, respectively.[34,36,37] Further evaluation of the use of FOLFOX in NET G3 is warranted. Overall, the response rates with platinum-based therapy for tumors with a Ki-67 index lower than 55% are lower than those of NEC/NET with a Ki-67 index higher than 55%, a finding that argues against the use of platinum-based therapy as the first-line treatment for NET G3 with low Ki-67 indices.

Temozolomide-Based Therapy

Temozolomide is a well-established therapy in metastatic, well-differentiated grade 1/2 pancreatic NET.[38-40] ECOG-ACRIN E2211, a randomized phase 2 study, evaluated temozolomide combined with capecitabine (CAPTEM) vs temozolomide monotherapy in 144 patients with grade 1 or 2 well-differentiated pancreatic NET. In the final analysis, the ORR was 39.7% in the combination arm vs 33.7% in the monotherapy arm, which translated into a difference in mPFS of 23.2 vs 15.1 months, respectively (hazard ratio [HR], 0.71; 95% CI, 0.46-1.07).[41] The difference between the 2 groups in the secondary endpoint of median OS (mOS) was not statistically significant; mOS was 53.8 months in the monotherapy arm vs 58.7 months in the combination arm (HR, 0.82; 95% CI, 0.51-1.33; P=.42). Similarly, the activity of CAPTEM in NET G3 has been shown in multiple studies. In a recent retrospective study done at Mayo Clinic, among patients with NET G3 who received CAPTEM, mPFS was 9.4 months and the ORR was 35%.[34]

Furthermore, a retrospective study from Australia reported the efficacy of CAPTEM in patients with metastatic, well-differentiated, intermediate- or high-grade NET. The 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 vs other subgroups. Similarly, temozolomide-based therapy (primarily CAPTEM) in a first-line setting resulted in an ORR of 28.6%, a DCR of 66.7%, and mPFS of 12.0 months in a recent multicenter retrospective study of 21 patients with NET G3.[36] In a retrospective study by Al-Toubah and colleagues of patients with advanced NEN treated with CAPTEM, results in those with well-differentiated grade 3 NET were significantly better than results in those with poorly differentiated grade 3 NEC (N=77; 38 NET and 39 NEC). When patients who had NET G3 were compared with those who had NEC, mPFS was 28 vs 7 months (*P*=.005), mOS was 36 vs 14 months (*P*=.001), and ORR was comparable (42% and 33%, respectively; *P*=.388).[42] As demonstrated by these studies, CAPTEM is considered a reasonable option in the first-line setting for patients with NEN G3.

Somatostatin Analogues

Given the high frequency of SSTR expression on NET G3 tumors, therapy with somatostatin analogues (SSAs) is reasonable.[13] No prospective trials have been performed, but substantial evidence suggests a benefit with the use of SSAs. A study evaluating 30 patients with progressive GEP-NET demonstrated a DCR (stable disease + partial/complete response) of 70% in those receiving an SSA.[43-45] A trial of an SSA is reasonable in highly selected patients with SSTR-positive G3 NET, but it is recommended that short-term (ie, 2-3 months) interval imaging be performed to assess disease biology.[13] The recently completed NETTER-2 trial used a 2:1 randomization to compare first-line peptide receptor radionucleotide therapy (PRRT) with a high-dose SSA (long-acting octreotide at 60 mg/mo administered intramuscularly). This study will provide important information on the efficacy of an SSA in NET G3.

Everolimus

The RADIANT trials established the use of everolimus in grade 1/2 GEP-NET by demonstrating improvement in mPFS.[35,37-39] The improvements in mPFS led to US Food and Drug Administration (FDA) approval of everolimus for patients with well-differentiated NET of gastrointestinal or lung origin.[35,46-48] An Italian study assessed everolimus in 15 patients with advanced NET G3 and a Ki-67 index of 55% or lower. Everolimus was used mainly in the second-line setting and resulted in mPFS of 6 months and mOS of 28 months.[49] Multiple other studies and case reports have concluded the benefit of everolimus in NET G3, but further prospective studies are warranted, such as EVINEC (NCT02113800).[50-52]

Sunitinib

Sunitinib is a tyrosine kinase inhibitor with anti-angiogenic properties that is FDA-approved for use in well-differentiated pancreatic NET.[53] A randomized, double-blind, placebo-controlled phase 3 study of sunitinib in patients with advanced well-differentiated pancreatic NET demonstrated an improved mPFS of 12.6 months in the sunitinib arm vs 5.8 in the placebo arm.[54] Limited data regarding GEP-NET G3 are based on an open-label, nonrandomized, prospective phase 2 trial of sunitinib that evaluated 31 patients, including 6 patients with NET G3. Approximately 13% of the patients had an objective response, with a DCR of 58%. However, because of the limited representation of patients with GEP-NET G3, no statistically significant benefit of sunitinib was seen in this patient population.[55] Similarly, in a Japanese retrospective study of 60 patients with pancreatic NEN, sunitinib was given with dose escalation in the absence of toxicities (maximum dose, 37.5 mg).[56] The ORR was 33.3%, and 48.3% of patients had stable disease. In the subset of 10 patients with NET G3, the ORR was 60%, and 30% of patients had stable disease. Despite the promising DCR, no patients derived benefit for a year or longer.[56] In a multivariate analysis of factors affecting PFS in this study, poor differentiation was the only significant factor associated with decreased PFS.[56] Given the small sample size, it is hard to justify the use of sunitinib in NET G3 at this time. A randomized phase 3 trial (CABINET) conducted by the Alliance for Clinical Trials in Oncology is evaluating cabozantinib (Cabometyx, Exelixis) in patients with well-differentiated NET, and patients with NET G3 are eligible. This trial should provide important information on the efficacy of kinase inhibitors in patients with NET G3.

Peptide Receptor Radionucleotide Therapy

PRRT has shown activity in multiple studies of well-differentiated NET that express SSTR.[29,57-60] The phase 3 NETTER-1 trial led to the approval of lutetium-177 (^{177}Lu)-dotatate for somatostatin-positive GEP-NET.[57] In patients with G1 or G2 small-bowel tumor, ^{177}Lu-dotatate showed a statistically significant mPFS benefit in comparison with high-dose, long-acting octreotide.[57] The ORR was 18% vs 3%, respectively (*P*<.001).[57] NET G3 generally expresses SSTR (87%-92% positivity rate on somatostatin receptor imaging) as well as ^{18}F-FDG avidity on PET owing to the intrinsically high rate of metabolic activity.[3,4,13] These features make PRRT a potentially relevant therapeutic option for patients

Table 2. Prospective Studies Evaluating Different Therapies for the Treatment of NEN G3

First Author	Tumor Characteristics	Study Type	No. Pts	Line of Treatment	Management Used	mOS, mo	mPFS, mo	ORR, %
Patel 2021[17]	NEN G3	Prospective cohort; multicenter phase 2	19	2nd	Ipilimumab and nivolumab	8.7	2	26
Zhang 2020[79]	GEP-NEC	Prospective phase 2	66	1st	Etoposide/ cisplatin vs irinotecan/ cisplatin	11.3 vs 10.2	6.4 vs 5.8	42.4 vs 42.4
Fottner 2019[99]	NEC and NET G3	Prospective, multicenter phase 2	27	2nd	Avelumab	NA	NA	NA
Morizane 2022[100]	NEC of GI tract	Prospective, multicenter phase 3	170	1st	Etoposide/ cisplatin vs irinotecan/ cisplatin	12.5 vs 10.9	5.6 vs 5.1	54.5 vs 52.5
Eads 2022 (EA2142)[81]	NEN G3	Prospective phase 2	67	1st	CAPTEM vs platinum/ etoposide	12.6 vs. 13.6	2.43 vs 5.36	9 vs 10
McNamara 2022[89]	Poorly differentiated extrapulmonary NEC	Prospective, multicenter phase 2	58	2nd	Liposomal irinotecan and 5-FU/folinic acid vs docetaxel	9 vs 5	32.1 vs 14.8	10.3 vs 10.3
Walter 2022[88]	NEC of GI tract	Prospective, multicenter phase 2	133	2nd	Bevacizumab/ FOLFIRI vs FOLFIRI	7 vs 8.9	3.7 vs 3.5	25.5 vs 18.3

5-FU, 5-fluorouracil; CAPTEM, capecitabine and temozolomide; FOLFIRI, leucovorin, 5-FU, and irinotecan; G3, grade 3; GEP, gastroenteropancreatic; GI, gastrointestinal; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; No., number; ORR, objective response rate; pts, patients.

with NET G3. In a recent study of 10 patients with NET G3 who received PRRT, the DCR was 70%, the ORR was 20%, and mPFS was 9.13 months (95% CI, 3.42 to not reached).[34] In another study, of 28 patients with NEN G3 (6 with Ki-67 >55% and 22 with Ki-67 ≤55%) receiving ^{177}Lu-based PRRT alongside chemotherapy (fluoropyrimidine or CAPTEM), the ORR was 35% and the DCR was 74%. mPFS was 9 months for the overall population, 12 months for patients with a Ki-67 index of 55% or lower, and 4 months for patients with a Ki-67 index higher than 55%. In addition, mOS was 46 months in the patients with a Ki-67 index of 55% or lower and 7 months in those with a Ki-67 index higher than 55%.[29] A European retrospective study demonstrated similar and promising outcomes with PRRT in a comparison of patients with NET G3 with those in an NEC cohort.[58] The mPFS and mOS for the patients with NET G3 were 19 and 44 months, respectively.[34,58] In addition, 2 retrospective studies showed similar activity of PRRT in patients with NET G3. Following PRRT in NET G3, the PFS appears to be between 11 to 18 months and OS has been reported to be up to 40 months, with substantial variation among published studies.[61,62] The efficacy of PRRT in patients with GEP-NET G2/G3 is currently being evaluated in the NETTER-2 trial, which is comparing the efficacy of ^{177}Lu-dotatate with that of high-dose (60 mg), long-acting octreotide in the first-line setting.[63]

Immunotherapy

Multiple trials have investigated the activity of programmed death ligand 1 (PD-L1) and programmed death 1 (PD-1) inhibitors in patients with NET, and the results have been disappointing. In the phase 2 KEYNOTE-158 study, pembrolizumab (Keytruda, Merck) in a cohort of 107 patients with well-differentiated (G1) or moderately differentiated (G2) NET showed limited activity, with an ORR of 3.7%, mPFS of 4.1 months, and mOS of

24.2 months.[64] It was not clear whether KEYNOTE-158 included patients with NET G3. The limited activity seen in KEYNOTE-158 could be partially explained by the overall low tumor mutational burden in well-differentiated pancreatic NET.[13,65] In contrast, patients with NEN G3, and more specifically NEC, have a higher mutational burden, which makes them a potential target for immune checkpoint inhibitors.[66,67] Pembrolizumab was evaluated in a small study of patients with NEN G3 previously treated with platinum-containing chemotherapy.[68] The ORR was only 5%; however, the cohort composition and differentiation were not reported.[68] The DART basket trial evaluated combination immunotherapy with ipilimumab (Yervoy, Bristol Myers Squibb; 1 mg/kg every 6 weeks) and nivolumab (Opdivo, Bristol Myers Squibb; 240 mg every 2 weeks) in patients with NEN G3,[69] 59% of whom (19/32) had NEN G3 of nonpancreatic origin (11 with NEC, 2 with NET G3, and 6 with unknown differentiation). The ORR was 26% (5/19) in the patients with NEN G3 vs no response in those with low/intermediate NET (Table 2).[70] All the responses were in patients with poorly differentiated neoplasms. The overall 6-month PFS rate was 32%, with mPFS of 2 months. The response durations for the 5 responders at the time of the last update were 8, at least 8, at least 11, at least 12, and 31 months. Similar preferential activity of checkpoint inhibitors in NEC in comparison with NET G3 was seen in a retrospective study evaluating the efficacy of dual checkpoint inhibitor therapy (ipilimumab and nivolumab) in 34 patients (27 NEC and 7 NET G3). The ORR was 14.7% and the DCR was 41.2%, with all responses seen in NEC.[71] Yet another retrospective study looked at checkpoint inhibitor monotherapy in patients with well-differentiated NET (all grades). In the 3 patients with NET G3, mPFS, OS, and time to next treatment were a modest 2.9, 15.4, and 3.8 months, respectively.[72] Overall, the role of immunotherapy in NET G3 is limited, and patients should ideally be enrolled in clinical trials of new immunotherapy combinations to help find combinations that may be more beneficial than those previously mentioned. It is worth mentioning that in the rare case of a mismatch repair–deficient tumor, the use of checkpoint inhibitors would be indicated.

In summary, SSAs can be considered for patients with a relatively indolent disease course. When a response is needed, CAPTEM can be considered. Similarly, other cytotoxic chemotherapies—such as FOLFOX and platinum/etoposide—can be considered, especially for patients with a higher Ki-67 index (ie, >55%). In addition, PRRT is an option for patients with SSTR-positive NET, particularly those with a lower Ki-67 index (ie, <55%).

Therapies for Extrapulmonary NEC

First-line Treatment

Because of a lack of data, much of the treatment for NEC has been extrapolated from studies of small cell lung cancer (SCLC).[73,74] Platinum-based chemotherapy (cisplatin or carboplatin) combined with etoposide has long been considered the standard of care on the basis of extrapolation from SCLC and multiple retrospective studies (eg, NORDIC and FFCD-GTE).[16,73,75,76] Overall, results from these retrospective studies suggest that first-line treatment with platinum/etoposide leads to an ORR of up to 50%, mPFS of 4 to 6 months, and mOS of 11 to 16 months.[3,14,16] The duration of treatment is not standardized in this setting, but one could consider 4 to 6 cycles of cisplatin or carboplatin and etoposide followed by close observation.[77] Although the NORDIC study demonstrated no differences in outcomes when carboplatin was used instead of cisplatin,[16] a recent Canadian registry study suggested that cisplatin is superior to carboplatin.[78] However, such differences are hard to delineate in a retrospective fashion, given selection bias. Hijioka and colleagues found that *RB* loss and *KRAS* mutations, which are more likely to be found in NEC, are predictive of response to platinum-based chemotherapy, a finding further supporting its use.[18]

Irinotecan has been suggested as an acceptable alternative to etoposide.[76] This was recently investigated in a Japanese phase 3 study of 170 patients with NEC comparing the effectiveness of irinotecan/cisplatin with that of platinum/etoposide (Table 2). mOS was comparable in the 2 arms, at 12.5 months with platinum/etoposide vs 10.9 months with irinotecan/cisplatin (HR, 1.04; 90% CI, 0.79-1.37; *P*=.80). Similarly, mPFS was 5.6 months in the platinum/etoposide group vs 5.1 months in the irinotecan/cisplatin group (HR, 1.06; 95% CI, 0.78-1.45).[79,80] Some differences in the frequency of adverse events were noted between the 2 groups in that diarrhea was more frequent in the irinotecan/cisplatin arm (47.6%) than in the platinum/etoposide arm (23.2%). On the other hand, febrile neutropenia occurred more frequently with platinum/etoposide (26.8%) than with irinotecan/cisplatin (12.2%). A smaller randomized phase 2 trial conducted in China yielded similar results.[79] Although the Japanese study was the first to compare these regimens in a prospective fashion, extrapolating the results to a Western population is challenging. Therefore, platinum/etoposide remains our standard of care in the United States.

Similarly, the phase 2 ECOG-ACRIN EA 2142 looked at CAPTEM vs platinum/etoposide in patients with NEN G3—either extrapulmonary NEC (excluding small cell histology) or NET G3.[81] The study was stopped

after a planned interim futility analysis showed CAPTEM not to be superior to platinum/etoposide (mOS of 12.6 vs 13.6 months, respectively). Of note, this study included both poorly differentiated and well-differentiated NEN G3, and outcomes for these subgroups have yet to be reported. However, it would be challenging to draw any conclusions for these subgroups, given the small sample size, although CAPTEM would be a possible alternative for patients who have severe neuropathy.[81]

Both atezolizumab (Tecentriq, Genentech) and durvalumab (Imfinzi, AstraZeneca) have shown marginal survival benefit when added to platinum-based chemotherapy in patients with SCLC.[82,83] On the other hand, adding pembrolizumab to platinum-based chemotherapy had no significant effect on OS, which raised into question the efficacy of adding PD-1/PD-L1 antibodies to platinum/etoposide in SCLC.[82] For that reason, along with recent literature suggesting molecular and immunologic differences between SCLC and GEP-NEC,[84] we argue that immunotherapy should not be added to first-line chemotherapy in NEC until more data are available. The ongoing SWOG 2012 trial is expected to answer that question (NCT05058651).

Second-line and Beyond

Cytotoxic Chemotherapy. After first-line platinum-based chemotherapy, no standard of care has been established. Patients who have a sustained response for more than 3 months after discontinuation of first-line platinum-based treatment may still be platinum-sensitive, and platinum/etoposide can be considered for use again.[16] CAPTEM is a reasonable second-line therapy after progression on prior platinum/etoposide, but the efficacy is brief, usually lasting less than 3 months.[85-87] In a study evaluating the efficacy of temozolomide combined with capecitabine and bevacizumab in patients with NEC after progression on platinum/etoposide, the ORR was 33%, mPFS was 6 months, and mOS was 22 months.[85] It is important to note that this study probably included both poorly differentiated and well-differentiated NEN G3, which explains the longer-than-expected PFS and OS. Furthermore, a retrospective analysis of 64 patients with NEC at Mayo Clinic examined the efficacy of second-line treatment with leucovorin, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX); leucovorin, 5-FU, and irinotecan (FOLFIRI); and CAPTEM. Across all regimens, mOS was 6.2 months and mPFS was 2.3 months. No statistically significant difference between either OS or PFS was found with the second-line regimens.[86] The above data, along with the established activity in the first-line setting, support CAPTEM as a possible second-line option in NEC.[41]

In the last year, 2 prospective studies evaluated the efficacy of irinotecan-based regimens in patients with NEC after progression on platinum/etoposide.[88,89] The phase 2 NET-02 study included 58 patients with NEC from multiple centers in the United Kingdom and randomly assigned them to either arm A, with the combination of 5-FU and liposomal irinotecan (nal-IRI), or arm B, with docetaxel. The primary endpoint was a 6-month PFS rate of at least 30%. Most patients (63%) had a gastrointestinal primary tumor, and 91% had disease resistant to first-line platinum-based treatment. With a median follow-up of 6.6 months, arm A (n=29) met the primary endpoint, with a 6-month PFS rate of 32.1%, an ORR of 10.3%, and mOS of 9 months. Arm B did not meet the primary endpoint.[89] More recently, the noncomparative phase 2 PRODIGE 41-BEVANEC study was reported at the European Society for Medical Oncology (ESMO) Congress 2022.[88] In this study, 133 patients with NEC and progression on prior platinum/etoposide were randomized to receive either bevacizumab at 5 mg/kg plus FOLFIRI or FOLFIRI alone, with a primary endpoint of 6-month OS rate of 50% or greater in the experimental arm. Most patients had NEC arising from the gastrointestinal tract (38 colorectal, 22 esophageal), and the rest had NEC arising from a pancreatic primary tumor (n=33) or an unknown primary tumor. The primary objective was met, with mPFS and mOS of 3.7 and 7 months, respectively, in the FOLFIRI/bevacizumab arm and mPFS and mOS of 3.5 months and 8.9 months, respectively, in the FOLFIRI arm. The ORR was 25.5% in the FOLFIRI/bevacizumab arm vs 18.3% in the FOLFIRI arm. The above data support irinotecan-based combinations as possible second-line therapy in patients with NEC, especially NEC arising from the gastrointestinal tract. Whether bevacizumab added any benefit is still unclear, so it should not be used routinely at this time.

The activity of the FOLFOX regimen has been previously investigated in patients with NEC. In a retrospective study of 17 patients with NEC, mainly of GEP or pulmonary origin, 5 patients had a partial response (ORR, 29%). mPFS was 4.5 months and mOS was 9.9 months.[90] Given the reasonable response to FOLFOX, it can be considered in the second-line setting. Although further studies are needed, combinations such as FOLFIRINOX and FOLFOXIRI can be considered for patients with NEC, especially if the primary tumor is pancreatic or colorectal. FOLFIRINOX is being compared with platinum/etoposide in the prospective randomized phase 2 FOLFIRINEC trial.[91] Lastly, a meta-analysis evaluated second-line chemotherapy options and found that temozolomide, topotecan, and everolimus produced an ORR of 0 when used as single agents, suggesting that single-agent therapy is not beneficial in NEC.[92]

Immunotherapy. Multiple studies have evaluated the activity of checkpoint inhibitors in high-grade NEN and shown an overall modest benefit with monotherapy, if any. Pembrolizumab was studied in a small group of patients with NEN G3 who had previously received platinum-containing chemotherapy.[68] The ORR was 5%, but the cohort composition was not reported. The anti–PD-1 antibody spartalizumab was evaluated in a trial in which multiple cohorts included patients with high-grade NEN.[93] Responses were poor, and it is unlikely that this drug will have significant activity as a single agent.[93] Similarly, Fottner and colleagues reported an interim analysis of the phase 2 AVENEC study evaluating the anti–PD-L1 antibody avelumab (Bavencio, EMD Serono/Pfizer) in 27 patients with advanced, metastatic, high-grade NEN G3 (16 NEC, 11 NET G3) that had progressed after first-line chemotherapy. The DCR after 8 weeks of treatment was 32%. In responders, the mean duration of disease control was 20 weeks, with 4 patients having stable disease or a partial response at 6 months or later.[94]

In contrast to the limited activity seen with monotherapy, dual checkpoint inhibition might have more activity in selected patients with NEC. As stated previously, the DART basket trial of nivolumab and ipilimumab showed an ORR of 26% (5/19) in patients with NEN G3, and all responses were in those with NEC.[69] A similar trend was seen in recent retrospective studies showing that only an unspecified subset of patients with NEC derived benefit from dual checkpoint inhibition.[71,95]

Combining checkpoint inhibitors with vascular endothelial growth factor (VEGF) inhibitors has shown significant benefit in a variety of tumors, including renal cell carcinoma and hepatocellular carcinoma. Similar efforts are being investigated in high-grade NEN. A recent phase 2 study evaluated the efficacy of the VEGF inhibitor surufatinib plus the PD-1 antibody toripalimab in 21 patients with advanced NEC refractory to first-line chemotherapy. The study showed promising activity, with an ORR of 20%, mPFS of 4.1 months, and mOS of 10.3 months.[96]

Of note, microsatellite instability (MSI) testing is recommended for patients with high-grade NEN, given the FDA tissue-agnostic indication for the use of dostarlimab (Jemperli, GSK) or pembrolizumab in patients with MSI-high malignancies regardless of origin.

Peptide Receptor Radionucleotide Therapy. The utility of PRRT in NEC is an area of uncertainty. Given the lower rate of expression of SSTR in NEC, if the receptor of interest is not expressed on somatostatin receptor imaging, then PRRT would be a moot point. Preliminary studies have shown effectiveness in aggressive-grade neoplasms with ^{18}F-FDG avidity and a concordant SSTR-expressing phenotype.[97] Sorbye and colleagues have advised that PRRT could be considered for patients with grade 3 GEP-NET or NEC, a Ki-67 index lower than 55%, and uptake demonstrated on somatostatin receptor imaging.[98] In a retrospective study of 29 patients with NEC treated with PRRT, mOS was 41 months for those with a Ki-67 index of 55% or lower but only 7 months for those with a Ki-67 index higher than 55%.[29] Thus, PRRT is a potential therapeutic option for patients with a Ki-67 index of 55% or lower.[29] An Australian-led multicenter, randomized phase 2 study is under development to examine the benefit of PRRT in patients with GEP-NEC. Unless more convincing data become available, the routine use of PRRT for NEC should be discouraged.

Conclusion

NEN G3 comprises a heterogeneous group of neoplasms in which prognosis and treatment depend on subgroup characteristics such as differentiation, proliferation rate, molecular profile, somatostatin receptor imaging uptake, and primary location. The 2017 World Health Organization guidelines dividing NEN G3 into NEC and NET G3 has provided clinicians who treat this disease with a better understanding of the prognosis and treatment for each entity. Separating NET G3 from NEC in future trials and cancer registries will continue to refine prognosis and selection of treatment. At this time, given the nuances of this disease, referral to a tertiary center remains of the utmost importance. A referral also allows expert pathologic review, which is critical for the reasons outlined in this article. Future trials are certainly needed, with special consideration given to the molecular heterogeneity of NEN G3.

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