Chapter 9
Systemic therapies: Chemotherapy and investigational agents

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Practice Points

- Platinum/etoposide chemotherapy should be considered as first-line treatment for patients with advanced Grade 3, poorly-differentiated neuroendocrine carcinomas (PDNECs).
- Later-line options for patients with advanced G3 PDNECs include FOLFOX, FOLFIRI and CAPTEM.
- Patients with G1-2 NENs tend to experience poor response rates from chemotherapy, with the possible exception of the CAPTEM regimen for pancreatic NENs.
- There is no consensus regarding optimal first-line therapy in patients with G3 well-differentiated NETs; treatment choice should be informed by the patient's comorbidities, tumour characteristics (such as the Ki-67 index) and PET imaging findings.
- Given the overall paucity of data to inform best practice and the limited efficacy of chemotherapy in G1-2 NENs, participation in clinical trials should be strongly encouraged where possible.

1. Introduction

NENs consist of a heterogeneous group of cancers that vary in behaviour and response to therapy. Gastroenteropancreatic NENs can be classified into Grade 1, 2 and 3 by the Ki-67 index and the mitotic rate (link to Table 1 in Chapter 2: Histopathology). As chemotherapy plays a very different role in the treatment of Grade 3 NENs compared to Grade 1-2 NENs, these two clinical situations will be discussed separately.

2. Grade 3 NECs / NETs

G3 NENs can be sub-classified, based on histological differentiation, into well-differentiated neuroendocrine tumours (NETs) and poorly-differentiated neuroendocrine carcinomas (NECs). NECs are poorly-differentiated, generally rapidly progressive, and associated with a poorer prognosis than NETs. Of note, well-differentiated grade 3 (G3) NENs, i.e. G3 NETs, are an evolving but distinct group themselves. G3 NETs differ from NECs, not only with respect to histology but also in epidemiology, clinical course, genomic alterations and response to therapy [1–3]. Given the reasonably recent sub-division of G3 NENs into G3 NETs and G3 NECs, there is limited prospective data regarding specific outcomes in the G3 NET subgroup.

NECs can be sub-typed as small cell or large cell type. Retrospective data have shown that these subtypes may vary in outcomes such as the objective response rate (ORR), median progression-free survival (PFS) and overall survival (OS) [4–8]. Regardless of the primary site, the choice of chemotherapy backbone is similar for patients with advanced G3 NECs.

A. First-line Chemotherapy in G3 NENs

Platinum (Cisplatin/carboplatin) and Etoposide

For non-pulmonary NECs, platinum doublet therapy (Cisplatin or Carboplatin coupled with etoposide) is generally used as the frontline therapy. Their initial use was based on extrapolation from the small cell lung cancer literature. Two large retrospective studies, the NORDIC-NEC [9] and a study by Yamaguchi et al. [10], have reported on the efficacy of platinum doublet therapy in patients with GEP-NECs. NORDIC-NEC reported favourable median overall survival with Cisplatin/Carboplatin and Etoposide chemotherapy (11 months) compared to best supportive care (BSC) alone (0.3-1.8 months)[9]. Yamaguchi et al showed comparable efficacy outcomes; multivariate analysis showed that hepatobiliary primary and elevated baseline lactate dehydrogenase were independent poor prognostic factors for OS [10]. These trials predominantly included patients with poorly-differentiated G3 NEC; whilst platinum doublets can be used in treatment of G3 NET, it is less clear as to whether they should be the first-line therapy of choice for G3 NETs.

Capecitabine and Temozolomide (CAPTEM) or temozolomide (TEM) alone

In a multicentre retrospective review of 118 patients with G3 GEPNENs, Chan et al. have reported response in 40% of patients treated with CAPTEM[16]. A large single-centre, retrospective, Australian study showed a trend towards improved PFS when CAPTEM was used upfront in untreated GEPNET patients instead of later line (17 versus 8 months, p = 0.30) or in patients with lower Ki-67 index (21-55%) (15 versus 4 months, p = 0.117)[17]. These trends may partially be explained by selection bias and the prognostic impact of a higher Ki-67 index. In another retrospective review of 25 G3 NEN patients receiving CAPTEM, mostly progressing on first-line therapy, showed a disease control rate of 71% with improved OS (12 vs 8 months, p=0.009) with treatment as compared to those without [18].

Given the increasing use of temozolomide-based treatment and its known association with O-6-methylguanine-DNA methyltransferase (MGMT) status in other tumour groups like glioblastoma, trials have investigated this relationship between MGMT status to the alkylating agent therapy in NET patients. Whilst the predictive role of MGMT status in NET patients remains controversial, a meta-analysis[19] by Qi et al. reported a 5-fold higher likelihood of response to alkylating agents in NEN patients with MGMT deficiency than those with proficient MGMT status (OR: 5.00; 95% CI: 3.04–8.22; $P < 0.001$; I^2: 3%).

There has been increasing evidence regarding the benefit of temozolomide-based regimens in some G3-NETs [17, 18, 20, 21]. There are several CAPTEM regimens used in the trials (***see Table 2***). Most Australian centres follow the regimen as suggested in the eviQ repository [22].

FOLFIRI/FOLFOX

FOLFIRI [16, 23–25] and FOLFOX [26] are other regimens that can be used based on retrospective data showing similar response rates to the above regimens (***see Figure 1***).

Cisplatin and Irinotecan

Several retrospective series [11–13] and small prospective phase II trials [14, 15] at Japanese centres have shown potential activity with first-line cisplatin/irinotecan. The corresponding response rates and survival outcomes from the trials have been summarised in ***Table 1***. Despite the benefit suggested in these earlier studies, the absence of phase III trials and confirmatory results from Western populations has limited the use of this combination in Australian centres to date.

B. Chemotherapy beyond the first-line setting

There is no level I evidence to guide subsequent therapy choice for patients with a G3 GEP NEN progressing on first-line therapy. Available chemotherapeutic options have shown disappointing response rates.

Various strategies have been employed in the published data. Options include rechallenging with the first-line treatment regimen (if the interval between chemotherapy cessation and progression is more than six months) or change to a second-line regimen. Second-line options include CAPTEM, FOLFOX (5-fluorouracil and oxaliplatin), FOLFIRI (5-fluorouracil, leucovorin, and irinotecan), Cyclophosphamide/doxorubicin/Vincristine (CAV) and topotecan alone based on retrospective studies.

Biomarkers for response to chemotherapy in G3 NENs

There is ongoing research in a bid to identify predictive biomarkers – that is, to identify patients who may respond better to a given therapy. Several candidate biomarkers have been investigated, including the Ki-67 index and Kirsten rat sarcoma viral oncogene mutation (mt-KRAS). A higher Ki-67 index, with proposed cut-offs of 60% or 55%, has been suggested as a potential biomarker to help predict for better response rates [27]. KRAS mutations and the loss of expression of *retinoblastoma* may also predict for the efficacy of platinum-based chemotherapy in this setting [10, 28]. Interestingly, the degree of differentiation has not been shown to influence the response rate to date [29–31].

An ongoing randomised trial, ECOG-ACRIN EA2142 (NCT02595424), is comparing upfront initial therapy with capecitabine plus temozolomide versus cisplatin plus etoposide in patients with advanced G3 non-small cell GEP NENs. This trial is expected to provide valuable data on the optimal sequencing of treatment regimens in this patient population.

3. Grade 1 or 2 metastatic NET

Somatostatin analogues are the mainstay of treatment for G1/G2 NETs. Whilst chemotherapy was classically used, specifically streptozocin- and 5-FU-based regimens, these have mostly been superseded by the development of other effective therapies (such as targeted therapies and PRRT) with better tolerance and arguably better efficacy in many scenarios.

A. Pancreatic NETs (pNETs)

Well-differentiated pNETs are more responsive to cytotoxic chemotherapy as compared to GI-NETs. There are several prospective [32] and retrospective [33] studies that have shown a favourable response rate. The most recent data comes from the exploratory two-arm, phase-II E2211-trial comparing CAPTEM versus TEM in patients (n =145) with progressive pNETs. It suggests superiority of CAPTEM compared with TEM alone - PFS (22.7 months versus 14.4 months, respectively; HR 0.58, P = 0.023)[34]. The ORR with TEM was similar to that in the CAPTEM arm (27.8 vs 33.3%).

B. Gastrointestinal NETs

The use of chemotherapy in G1-2 (non-pancreatic) GI NETs is a matter of ongoing debate. As per published data, the response rates with chemotherapy in the advanced well-differentiated NETs are low, for example, the ORR in advanced well-differentiated G1/G2, non-pancreatic GI NETs was 11.5% (range 5.8%-17.2%) [35]. The potential use of chemotherapy in subsequent line therapy is decided on a case-by-case basis. ESMO guidelines recommend consideration of chemotherapy in patients with "higher probability of response (higher Ki-67 in the range of 15%-20%; significant progression)"[36–38]. The limited adoption of chemotherapy for G1-2 NET in Australian centres, is primarily due to slow rate of progression, the availability of other, relatively less-toxic drugs (such as SSAs) and use of targeted agents on progression. Further, no randomised trial has shown a statistically significant improvement in PFS or OS over best supportive care.

C. Streptozocin (Streptozotocin)-based regimens

Streptozocin-based regimens have been traditionally used in the care of patients with pancreatic NETs (pNETs). A randomised phase III study by Moertel et al. in 1992 showed an advantage for streptozocin and doxorubicin over streptozocin and 5-FU doublet with impressive response rate (69% vs 45%; P = 0.05), response duration (20 vs 6.9 months; P = 0.001) and median OS (26 vs 18 months; P = 0.004)[39]. While streptozocin-based therapies are active in patients with advanced pNETs, these regimens have not been used as much in the Australian setting, largely due to practical considerations including a relatively cumbersome administration schedule and increased toxicity profile including myelosuppression, nausea, alopecia, and renal dysfunction. With retrospective data suggesting that temozolomide-based combinations have at least similar activity, especially in pNETs [40], temozolomide-based combinations have largely superseded streptozocin-based regimens.

4. Investigational treatments

A large number of strategies, including the use of chemotherapy, immunotherapy alone and in combination, are being investigated in current trials. NABNEC [41] is a phase II study, comparing two chemotherapy regimens (carboplatin/nab-paclitaxel versus carboplatin/etoposide) as first-line treatment in GI-NEC, recruiting in Australian centres. Whilst it has recently been amended to a single-arm design, it will hopefully still establish the role of carboplatin/nab-paclitaxel in the treatment paradigm of advanced gastrointestinal NECs. In addition, it explores translational biologic, molecular and functional imaging endpoints to inform future research and improve outcomes for NEC patients.

Immunotherapy trials are still in progress and data is immature, although response rates with immunotherapy alone have been disappointing to date. Single-agent checkpoint inhibitor drugs like Pembrolizumab [42, 43] and Spartalizumab [44, 45] suggest that anti-programmed cell death 1 (PD-1) drugs may have limited activity as single-agent therapy. There is little evidence regarding the use of immunotherapy in G3 GEP NENs to date. Other trials are seeking to explore the role of various chemotherapy[46] and immunotherapy agents (like pembrolizumab[47], nivolumab[47], ipilimumab[47], avelumab[48]) in combination or alone to fully explore the potential benefit of available drugs similar to that achieved in other diseases. More recently early results of chemo-immunotherapy trials (i.e. addition of PDL1 inhibitors to the chemotherapy-backbone) have shown superior outcomes [29] in patients with small cell lung cancer (SCLC). For example, an initial report of the trial using Atezolizumab has shown landmark rates of PFS (12.6 vs 5.4%), OS (51.7 vs 38.2%) at 12 months [49]. Though the optimal duration of treatment is not established, generally four cycles of induction chemo-immunotherapy are followed by maintenance immunotherapy. There are other ongoing trials combining chemotherapy with immunotherapy [44, 50] that will inform future practice and research.

5. Recommendations

Chemotherapy regimens and its use should be individualised based on the clinical picture, tumour characteristics, rate of progression and in line with patient wishes.

1st line

- G3-NEN
    - G3 NECs - Chemotherapy would be the appropriate first-line treatment for patients with advanced NEC. In line with latest ESMO (2020)/ENETs (2016) and other major guidelines, we agree with the recommendation of:
        - Platinum (cisplatin/carboplatin) with etoposide in patients with high-grade small- or large-cell G3 NEC, irrespective of the primary tumour origin, with liver and/or other distant metastases.
        - Alternatives include FOLFOX and FOLFIRI regimens.
        - Given the modest median OS (11-19 months) despite high ORR (30%-67%), participation in clinical trials should be encouraged.
    - G3 NET – The chemotherapy regimen needs to be adapted to the patient's co-morbidities and tumour characteristics. Unlike G3 NEC, platinum doublet chemotherapy is not necessarily the first-line regimen of choice.
        - Appropriate to consider CAPTEM regimen (or a platinum doublet) as one of the options for upfront chemotherapy especially for patients with lower Ki-67 indices (<55%).
        - Due consideration needs to be given to other options, including single agent-TEM, targeted agents, Lutetium-177 Peptide Receptor Radionuclide Therapy in the case of pNETs.
    - Some institutions [51] suggest an algorithm for chemotherapy choice based on the Ki-67 index as seen in ***Figure 1***.

- G1/2 NEN
    - Systemic chemotherapy should be individualised for patients.
    - Upfront chemotherapy not recommended for slowly progressing G1/2 well-differentiated GI-NETs.
    - Chemotherapy may be considered for NET G2 with higher Ki-67 (close to NET G3) or showing rapid clinical progression.
    - Regimens include combination chemotherapy (CAPTEM) or single agents (TEM alone).
        - The use of MGMT status to pre-select patients for TEM is not recommended at present or funded under PBS.
        - Single-agent therapy could be considered for patients with slower progression and combination therapy for fitter patients.
        - Other regimens may include (infusional 5-FU) or streptozocin-based regimens, but these are less used in G1/2 NEN in practice.

Later lines

- Given the paucity of data and low response rates, in general, there is no recommended second-line therapy and enrolment in available trials is highly recommended.
- Different regimen options (including CAPTEM, FOLFIRI, FOLFOX) may be considered for NETs.
    - Since the data to support their use largely consists of small single-centre studies, the treatment should be individualised to tumour characteristics, patient preference and co-morbidities.

Tables

Table 1: Selected trials in Grade 3 GEP-NENs [48]

Table 2
Selected trials in grade 3 gastroenteropancreatic neuroendocrine tumors

Trial Name	Histology (No. Patients Treated)	Regimen	Response Rate, %	Overall Survival, mo
1. First-line studies				
Moertel et al,[29] 1991	"Anaplastic neuroendocrine carcinoma" (18)	Cisplatin/etoposide	67	19.0
Mitry et al,[28] 1999	PDNEC (41)	Cisplatin/etoposide	42	15.0
Sorbye et al,[30] 2013	GEPNEN (252)	Mostly cisplatin/ etoposide or carboplatin/ etoposide	31	11.0
Yamaguchi et al,[34] 2014	PDNEC, MiNEN, or clinical NEC (258)	Cisplatin/etoposide Cisplatin/irinotecan	28 50	7.3 13.0
Nakano et al,[35] 2012	PDNEC (28 first-line, 16 second-line or beyond)	Cisplatin/irinotecan	50	16.0
Du et al,[42] 2013	GEPNEC (11)	FOLFIRI	64	13.0
Bajetta et al,[43] 2007	PDNEC (13)	XELOX	23	5.0
Walter et al,[44] 2017	GEPNEC (152)	Platinum/etoposide (cisplatin in 113, carboplatin in 39)	50	11.6
2. Second (and subsequent)-line studies				
Hentic et al,[45] 2012	G3 NEC (19)	FOLFIRI	31	18.0
Hadoux et al,[46] 2015	G3 PDNEC (20; 12 GEPNEC, 4 thoracic)	FOLFOX	29	9.9
Welin et al,[39] 2011	PDNEC (25)	Temozolomide, CAPTEM, some with bevacizumab	33	22.0

For trials before 2010, poorly differentiated tumors (and relevant subgroups from trials investigating wide populations) were used as a surrogate for G3 disease.

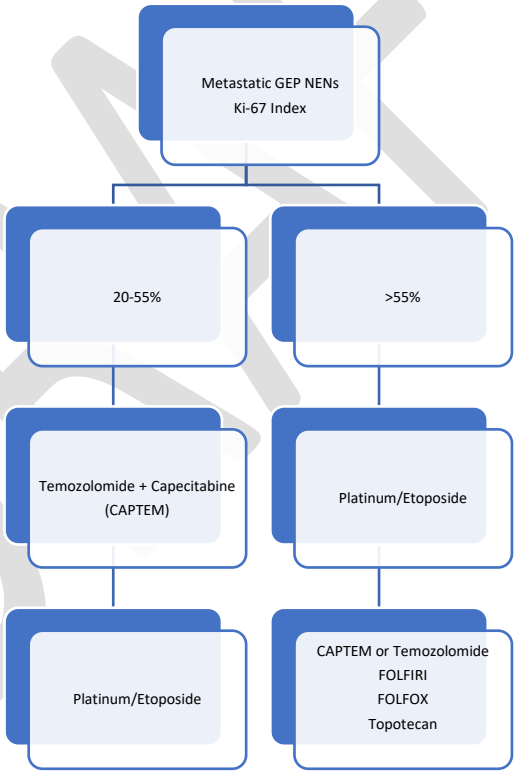
Abbreviations: CAPTEM, capecitabine; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; G3, grade 3; GEPNEC, gastroenteropancreatic neuroendocrine carcinoma; GEPNEN, gastroenteropancreatic neuroendocrine neoplasm; MiNEN, mixed neuroendocrine-nonneuroendocrine neoplasms; NEC, neuroendocrine carcinoma; PDNEC, poorly differentiated pancreatic neuroendocrine carcinoma; XELOX, capecitabine/oxaliplatin.

Table 2: Capecitabine and temozolomide regimens

Frequency	Capecitabine Dose	Temozolomide	Reference
28 days	750 mg/m^2 TWICE a day *(Cap dose at 2500 mg/day) d1 to 14	100 mg/m^2 TWICE a day d10-14	Eviq [22]
28 days	750 mg/m^2 BD d1-14 q28d	150-200 mg/m^2 ONCE a day d10-14	de Mestier et al 2020 [52]
28 days	600 mg/m^2 BD d1-14	75 to 100 mg/m^2 BD d10-14.	Abbasi et al 2014[53]
28 days	1000 mg BD d1-14 q28d	100 mg/m^2 BD d10-14	Saif et al 2013[54]

Figures

Figure 1: Suggested algorithm for chemotherapy choice based on the Ki-67 Index [55]



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