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Neuroendocrine Cancers (JR Strosberg, Section Editor)

The Role of Cytotoxic Chemotherapy in Well-Differentiated Gastroenteropancreatic and Lung Neuroendocrine Tumors

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Opinion Statement

The treatment landscape of well-differentiated neuroendocrine tumors (NETs) has considerably expanded in recent years, and both somatostatin analogs, radiolabeled somatostatin analogs, everolimus, and sunitinib have been incorporated within the therapeutic armamentarium against these malignancies. Even in the context of multiple treatment options available, cytotoxic chemotherapy plays a pivotal role in the management of pancreatic NETs (panNETs), while its activity in midgut carcinoids and lung NETs is still debated. High response rates, ranging from 30 to 70%, have been consistently reported in studies of panNETs investigating streptozotocin-, temozolomide-, or platinum-based regimens, and an unprecedented prolongation of progression-free survival has been recently demonstrated in a prospective, randomized trial of capecitabine and

temozolomide in patients with progressive panNETs. As a general principle, cytotoxic chemotherapy appears particularly appropriate in patients with bulky, symptomatic, or rapidly progressing tumors, especially of pancreatic origin, or in the salvage setting of NET patients who have failed alternative therapeutic options. Emerging evidence has also shown the potential efficacy of induction chemotherapy in patients with locally advanced or oligometastatic panNET, but prospective validation is needed before implementation of this approach in routine clinical practice. At present, there is no consensus on adjuvant therapy in pulmonary NETs, and differences between guideline recommendations at this regard mainly stem from the lack of high-level evidence. In the future, the identification of molecular biomarkers of response to chemotherapy might allow better patient preselection, thus leading to improved outcomes.

Introduction

Neuroendocrine tumors (NETs) are heterogeneous neoplasms arising from secretory cells of the diffuse neuroendocrine system. Although they may develop in any organ, NETs predominate within the gastroenteropancreatic (GEP) tract and the bronchopulmonary (BP) tree [1]. The incidence of NETs has been steadily rising in the last four decades, and NETs currently constitute the second most common neoplasm of the gastrointestinal system [2•]. The clinical behavior of NETs is critically influenced by both primary site and grade, among other factors [1]. While metastatic small-bowel NETs are usually characterized by an indolent growth and the ability to secrete serotonin and other vasoactive substances, pancreatic NETs (panNETs) and BP-NETs tend to behave more aggressively, often in the absence of a hormonal output. According to the 2017 World Health Organization (WHO) classification, panNETs are subdivided as either well-differentiated (low-grade, intermediate-grade, or high-grade) tumors or poorly differentiated (high-grade) carcinomas [3••]. Similar classifications are currently adopted for midgut carcinoids and BP-NETs, although poorly differentiated neuroendocrine carcinomas (NECs) are always considered equivalent to G3 neoplasms in these tumor entities [4, 5].

The therapeutic landscape of well-differentiated NETs has substantially expanded in recent years. Beyond somatostatin analogs [6, 7], radiolabeled somatostatin analogs have been approved for the treatment of GEP-NETs [8]. The mTOR inhibitor everolimus has demonstrated antitumor activity against a broad spectrum of pancreatic and extra-pancreatic NETs [9, 10], while the antiangiogenic agent sunitinib has shown efficacy in panNETs [11]. Despite relative absence of high-level evidence of activity, cytotoxic drugs remain an essential component of the therapeutic armamentarium against NETs. Alkylating agents including streptozocin (STZ), dacarbazine (DTIC), and temozolomide (TEM), antimetabolites such as 5-fluorouracil (5-FU) and capecitabine (CAP) and topoisomerase inhibitors such as etoposide as well as platinum derivatives have been consistently associated with high response rates in both panNETs and poorly differentiated NECs, while modest or negligible activity has been observed in foregut and midgut carcinoids respectively.

Here, we summarize the most recent studies on cytotoxic agents in both GEP- and BP-NETs, focusing on the role of chemotherapy in tumors with well-differentiated histology.

Chemotherapeutic agents in NETs: an overview

Two major classes of cytotoxic drugs are primarily used to treat well-differentiated NETs: alkylating agents and antimetabolites. The alkylator STZ

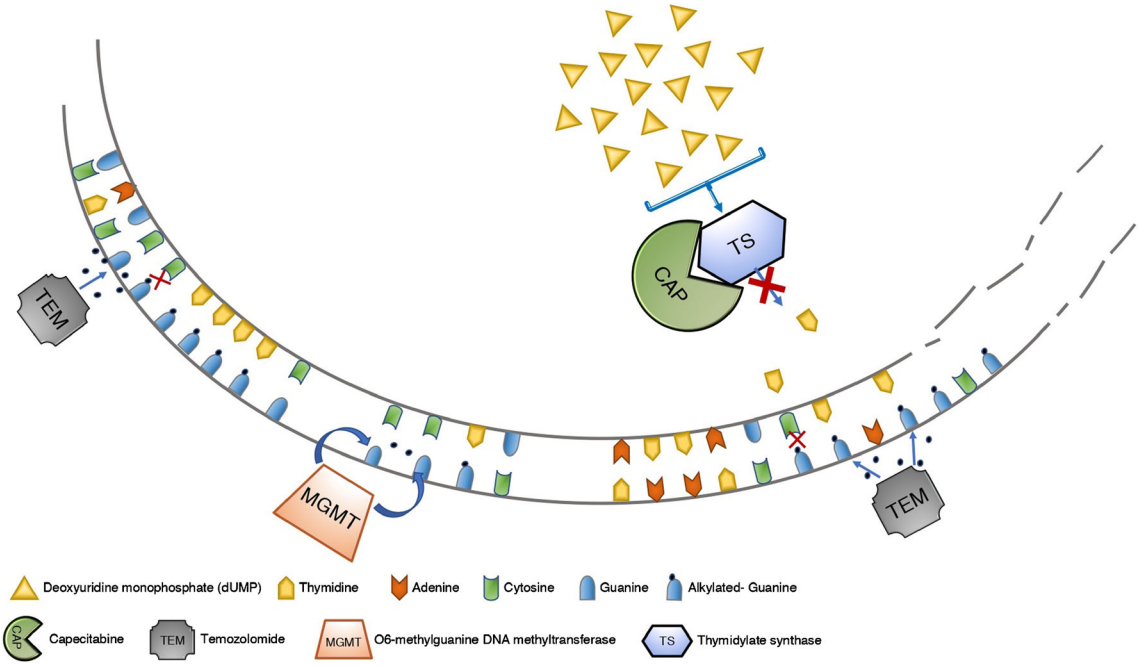

Fig. 1. Schematic representation of the cytotoxic effect induced by temozolomide in cancer cells. (Left) Temozolomide exerts its cytotoxic activity by alkylating the O^6 position of guanine residues. The O^6-methylguanine is misread by mismatch repair enzymes as an adenosine base, and thymidine is inserted in place of a cytidine on the opposite DNA strand. This results in repeated thymidine:cytidine mismatches, thus leading to thymidine depletion. (Middle) The suicide enzyme O^6-methylguanine DNA methyltransferase (MGMT) counteracts the effects of temozolomide by removing the alkyl groups from guanine residues. Therefore, the deficiency of MGMT enhances the sensitivity of cancer cells to alkylators. (Right) Both capecitabine and temozolomide synergistically deplete the intracellular thymidine pool: while capecitabine directly inhibits the thymidylate synthase enzyme, thus reducing the production of thymidine, temozolomide induces the accumulation of thymidine residues within the DNA double helix, eventually contributing to thymidine depletion and DNA breaks

is a glucose analog and is selectively incorporated into the β cells of the pancreas via GLUT2 transporters. Following intracellular accumulation, STZ induces the formation of DNA adducts, leading to cell death. Apart from β cells, GLUT2 transporters are expressed in the liver and in the kidney, and it is therefore not surprising that STZ toxicities may commonly involve these organs [12]. In clinical trials of NET patients, STZ has been often combined with 5-FU or doxorubicin. However, the use of doxorubicin has been progressively decreasing in recent years, as a result of the cardiotoxicity of this anthracycline. Two STZ/5-FU schedules are currently used in the clinical setting, and they include the Moertel protocol (500 mg/m^2 of STZ plus 400 mg/m^2 of 5-FU on day 1–5 every 6 weeks) and the Uppsala protocol (500 mg/m^2 of STZ on days 1–5 and 400 mg/m^2 of 5-FU on days 1–3 followed by 1-day infusion of 1,000 mg/m^2 of STZ and 400 mg/m^2 of 5-FU, repeated every 3 weeks) [13, 14].

DTIC is a non-classic synthetic alkylator. Its active metabolite 5-(3-methyltriazeno) imidazole-4-carboxamide (MTIC) alkylates and methylates the DNA primarily at the N^7 or O^6 position of guanine residues, thus causing base pair mismatch, DNA single- and double-strand breaks, and consequently apoptosis. DTIC has been used either as monotherapy or in combination with 5-FU and

Table 1. Cytotoxic chemotherapy in panNETs: efficacy results from major studies

Chemotherapeutic backbone	Regimen	Study type	Patients (*n*)	ORR (%)	PFS (months)	OS (months)	Ref.
STZ-based combinations	STZ vs STZ + 5-FU	Prospective	84 (42 vs 42)	36 vs 63	NR	16.5 vs 26	16
	STZ + 5-FU vs STZ + doxorubicin vs chlorozotocin	Prospective	105 (34 vs 38 vs 33)	45 vs 69 vs 30	6.9 vs 20 vs 6.9	18 vs 26.4 vs 16.8	17
	STZ + 5-FU + cisplatin	Prospective	47	38	NR	NR	24
	STZ + doxorubicin	Retrospective	45	36	16	24	18
	STZ + liposomal doxorubicin	Retrospective	30	40	13	52	19
	STZ + 5-FU	Retrospective	96	43	NR (TTP: 19.4 months)	54.8	20
	STZ + 5-FU	Retrospective	133	28	23	51.9	22
	STZ + 5-FU + doxorubicin	Retrospective	84	39	18	37	23
	STZ + doxorubicin or STZ + 5-FU	Retrospective	65	34	NR	NR	21
	STZ or STZ + Doxo or STZ + 5FU	Retrospective	110	22	9.8	NR	25
DTIC-based combinations	DTIC (high dose)	Prospective	50	33	NR	19.3	26
	DTIC + 5-FU + epirubicin	Prospective	28	28*	NR (TTP: 21)	38	28
	DTIC + 5FU + epirubicin	Prospective	15	27	NR	NR	29
	DTIC	Retrospective	50	32	10	NR	27
	DTIC + 5FU + epirubicin	Retrospective	16	58	17	27	30
TEM-based combinations	TEM vs CAPTEM	Prospective	144 (72 vs 72)	28 vs 33	14.1 vs 22.7	38 vs not reached	45
	TEM + thalidomide	Prospective	11	45	NR	NR	33
	TEM + bevacizumab	Prospective	15	33	14.3	41.7	34
	TEM + everolimus	Prospective	40	40	15.4	Not reached	35
	CAPTEM	Prospective	30	70	18	Not reached	36
	CAPTEM	Prospective	12	61 (in the entire cohort of 18 patients)	14 (in the entire cohort of 18 patients)	83 (in the entire cohort of 18 patients)	15

Table 1. (Continued)

Chemotherapeutic backbone	Regimen	Study type	Patients (*n*)	ORR (%)	PFS (months)	OS (months)	Ref.
	CAPTEM	Prospective	46	52	18.4	38.3	38
	^{177}Lu-Octreotate + CAPTEM	Prospective	30	80	48	Not reached	47
	TEM	Retrospective	12	8	NR (TTP: 7 months)	NR	32
	CAPTEM	Retrospective	143	54	17	73.2	37
	CAPTEM	Retrospective	21	57	16.5	NR	40
	CAPTEM	Retrospective	14	47[#] (in the entire cohort of 32 patients)	10 (in the entire cohort of 32 patients)	24 (in the entire cohort of 32 patients)	41
	TEM or CAPTEM	Retrospective	43	40	20	NR	39
	TEM or CAPTEM	Retrospective	43	27 (in the entire cohort of 95 patients)	13 months	35 months	43
	CAPTEM vs DTIC + 5-FU	Retrospective	138 vs 66	46 vs 48	23.1 vs 12.8	64.3 vs 59.3	42
Platinum-based combinations	XELOX	Prospective	11	27	NR	NR	48
	XELOX + bevacizumab vs FOLFOX + bevacizumab	Prospective	16 vs 12	19 vs 50	15.7 vs 21	38 vs 31	71
	GEMOX	Retrospective	37	38	7.3	25.7	49
	XELOX or FOLFOX-6 or GEMOX	Retrospective	36	33	8 (in the entire cohort of 78 patients)	32 (in the entire cohort of 78 patients)	50

*In the whole enrolled cohort, not in the specified tumor subgroup; [#]ORR by PERCIST 1.0 response criteria
panNET, pancreatic neuroendocrine tumor; *ORR*, overall response rate; *PFS*, progression-free survival; *OS*, overall survival; *NR*, not reported; *STZ*, streptozotocin; *5-FU*, 5-fluorouracil; *TTP*: time-to-progression; *DTIC*, dacarbazine; *TEM*, temozolomide; *CAPTEM*, capecitabine plus temozolomide; *XELOX*, capecitabine plus oxaliplatin; *GEMOX*, gemcitabine plus oxaliplatin

epirubicin for the treatment of NETs. Treatment with single-agent DTIC was better tolerated than the combination regimen, and the most severe toxicities included nausea, vomiting, and diarrhea [12].

TEM is an oral alkylating agent derivative of DTIC, with which it shares the active metabolite MTIC. TEM has been investigated either in monotherapy or in combination with other cytotoxic or targeted agents in patients with NETs, and one of the most effective regimens, CAPTEM, is represented by the combination of TEM with the oral fluoropyrimidine CAP. Mechanistically, the observed synergistic activity of CAP and TEM is related to the depletion of the intracellular thymidine pools exerted by both drugs. Indeed, while CAP directly reduces thymidine pools through inhibition of thymidylate synthase, TEM induces repeated thymidine:cytidine mismatches in the DNA double helix, eventually contributing to thymidine depletion [15] (Fig. 1). Common side effects of TEM include fatigue and thrombocytopenia, while palmar-plantar erythrodysesthesia, nausea, vomiting, and diarrhea are the main toxicities related to CAP.

Oxaliplatin is a coordination complex of platinum and damages the DNA with a mechanism similar to alkylating agents. The drug penetrates the plasma membrane through the Cu^{2+} transporter and once in the cytoplasm it generates positively charged reactive intermediates that bind nucleophilic sites of DNA, thus inducing cross-links in the DNA strands. Toxicities from oxaliplatin include nausea, vomiting, diarrhea, fatigue, stomatitis, and peripheral neuropathy.

The role of chemotherapy in panNETs

PanNETs are substantially more sensitive to cytotoxic drugs as compared with NETs from other primary sites, probably as a result of differential expression of DNA repair enzymes, genomic background, and cell cycle kinetics. Most of the studies of chemotherapy in panNETs were carried out during the 1980s and 1990s, and therefore anteceded both the evolution of the modern classification of NETs as well as the introduction of objective radiological criteria. For such reasons, and in light of their frequently underpowered nature, historical studies of chemotherapy in panNETs should be interpreted with caution. Cytotoxic drugs have been investigated in both the advanced and preoperative setting in patients with panNETs.

Advanced setting

STZ has consistently shown antitumor activity in clinical trials of patients with metastatic panNETs (Table 1). In a study sponsored by the Eastern Cooperative Oncology Group (ECOG) [16], 84 patients with advanced panNET were randomized to receive STZ in monotherapy or in combination with 5-FU, and a response rate of 36% and 63% respectively was reported. Given the encouraging results obtained in the combination group, a subsequent three-arm study investigated the efficacy of STZ plus 5-FU versus STZ plus doxorubicin versus chlorozotocin in 105 patients with panNETs [17]. The combination of STZ and doxorubicin was found to be associated with a response rate of 69% and a time to tumor progression (TTP) of 20 months, whereas the response rates associated

with STZ/5-FU and chlorozotocin were 45% and 30%, respectively, in the presence of a similar TTP of 7 months. The antitumor activity of STZ-based combinations in panNETs has been confirmed by a number of modern retrospective studies that have shown objective response rates (ORR) up to 40% [18–25]. Nausea, renal insufficiency, and myelosuppression are the main toxicities related to the treatment with STZ.

High-dose DTIC (850 mg/m^2 every 4 weeks) has been investigated in a phase II study sponsored by ECOG that enrolled patients with advanced panNETs [26]. The trial reported an ORR of 33% among the 42 subjects with measurable disease, in the presence of a median OS of 19 months. However, grade 3 and 4 toxicities were relatively common, and two treatment-related deaths were reported on trial. In a retrospective series of 50 patients with well-differentiated progressive panNETs, monotherapy with DTIC at 650 mg/m^2 every 4 weeks was associated with a response rate and a disease-control rate (DCR) of 32% and 66%, respectively, while the progression-free survival (PFS) was 10 months [27]. In contrast with high-dose DTIC, lower dosages of this alkylator were associated with manageable side effects primarily including nausea and vomiting. Different studies have assessed the safety and efficacy of DTIC in combination with 5-FU and epirubicin, reporting response rates between 18 and 44% in patients with advanced, progressive panNETs [28–31]. At present, the clinical use of DTIC-based combinations is limited by the severe toxicities induced by these regimens.

TEM, either alone or in combination, has recently emerged as an active and tolerable agent for the treatment of panNETs. Data on the efficacy of TEM monotherapy mainly derive from retrospective studies, with one of the largest series enrolling only 12 heavily pretreated patients with metastatic panNET. In this study, disease control was reported in 9/12 patients, and thrombocytopenia was the most common grade 3 side effect, being observed in 14% of cases [32]. Subsequent studies have investigated the efficacy of TEM in association with either targeted drugs, cytotoxic agents, or peptide receptor radionuclide therapy (PRRT). In a phase II trial enrolling 29 patients with NETs, the combination of TEM and the antiangiogenic agent thalidomide demonstrated an ORR of 45% in the subset of 11 patients with panNETs, with a median duration of response of 13.5 months [33]. TEM has been also studied in combination with the anti-VEGF mAb bevacizumab in a phase II study accruing 34 heavily pretreated patients with NETs from different primary sites. Among the 15 patients with panNETs, the ORR was 33% and the median PFS was 14.3 months [34]. Promising results have been also reported in a phase I/II study investigating TEM plus the mTOR inhibitor everolimus in a population of 40 patients with advanced panNETs. While the median PFS was 15.4 months, the ORR and disease-control rate were 40% and 93% respectively [35].

The CAPTEM regimen has been recently evaluated in both retrospective and prospective studies of advanced panNETs. In a single-institution series of 30 chemonaïve patients with panNET, CAPTEM induced objective responses in 70% of cases and was associated with a median PFS of 18 months, with grade 3/4 toxicities occurring in 12% of patients [36]. Similar results have been reported in subsequent studies, showing an ORR up to 60% [15, 37–43]. An ECOG-sponsored, prospective, randomized, phase II trial [44••] has recently investigated temozolomide alone versus CAPTEM in 144 patients with progressive, G1/G2 panNETs. A significantly improved median PFS was recorded in the

combination arm with respect to the monotherapy arm (22.7 months vs 14.4 months respectively; hazard ratio 0.58, $p = 0.023$). Consistent with PFS data, the median OS was 38 months in patients receiving temozolomide alone, while it was not reached in patients treated with CAPTEM (hazard ratio 0.41, $p = 0.012$).

TEM has been also tested, alone or in combination with CAP, as a radiosensitizer in patients undergoing PRRT. The concurrent administration of CAPTEM and ^{177}Lu-Octreotate did not alter the biodistribution and dosimetry of radiolabeled somatostatin analogs [45], and the combined chemo-radionuclide therapy showed a manageable toxicity profile [46]. In a phase II study enrolling 30 patients with advanced, progressive, well-differentiated panNET, concurrent treatment with ^{177}Lu-Octreotate and CAPTEM induced an ORR of 80% a median PFS of 48 months [47]. The long-term effects of chemo-radionuclide therapy on the induction of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) need careful prospective evaluation before implementation of the association regimen in routine clinical practice.

Several studies have investigated oxaliplatin-based combinations in patients with advanced panNET. A phase II trial investigated capecitabine and oxaliplatin (XELOX) in 27 patients with well-differentiated NETs progressive to first-line somatostatin analogs. Among 11 patients with panNETs, partial responses and disease stabilization were observed in 27% and 45% of cases respectively [48]. The combination of gemcitabine and oxaliplatin (GEMOX) was assessed in a retrospective series of 104 patients with metastatic NETs. After a median of 6 treatment cycles, GEMOX showed an ORR of 38% and a median PFS of 7.3 months among patients with panNETs [49]. A retrospective, multi-center series of 78 patients with NETs assessed the efficacy of oxaliplatin-based chemotherapies including XELOX, GEMOX, and FOLFOX (5-FU, leucovorin, oxaliplatin). Overall, the ORR was 33% among the 36 patients with panNET, while neuropathy and diarrhea were the most commonly observed severe toxicities [50].

At present, with the exception of the ECOG E2211 trial [44••], there are no studies prospectively comparing different chemotherapy regimens in patients with well-differentiated panNETs. As result, there is no definite evidence to guide chemotherapy choice. CAPTEM and STZ/5-FU represent the most used regimens in clinical practice, but it is currently unknown whether the first should be preferred over the second, or vice versa. Additionally, no studies have compared so far cytotoxic drugs versus targeted agents in panNET patients, and no sequencing strategies have been therefore validated. The two-arm, randomized, phase III SEQTOR study is currently investigating whether the sequence of STZ/5-FU followed by everolimus at tumor progression has a better efficacy profile with respect to the sequential treatment with everolimus followed by STZ/5-FU (NCT02246127). The study has completed accrual, and results are awaited soon.

Preoperative setting

Tumor downsizing by neoadjuvant treatment facilitates surgery and may have a positive impact on the rates of curative resections. Although induction therapy is currently not considered standard of care for the treatment of locally advanced/oligometastatic panNETs, evidence of its potential utility in selected clinical scenarios is presently growing. A number of chemotherapy regimens

have been investigated as preoperative treatment in patients with well-differentiated panNETs, but evidence of activity derives only from relatively small retrospective series. In a study evaluating 46 patients with synchronous panNET liver metastases who were candidates for radical resection, both OS and relapse-free survival (RFS) were significantly improved in patients who underwent preoperative chemotherapy with 5-FU, doxorubicin, and STZ (FAS regimen) as compared with patients who underwent surgery alone [51•]. In another retrospective series of 42 patients with low-to-intermediate grade, advanced panNETs, preoperative treatment with different chemotherapeutic regimens led to tumor shrinkage and subsequent surgery in 67% of cases, with a rate of R0 and R1 resections of 46% and 21% respectively. Although generally safe, pancreatic surgery following neoadjuvant chemotherapy was associated with one perioperative death and severe complications in 5 patients [52]. Disappointing debulking results have been instead reported in another study of 28 patients with locally advanced panNET who received preoperative FAS [53].

Table 2. Recommendations for the treatment of BP-NETs in the adjuvant and metastatic setting: an overview from major cooperative oncology group guidelines

Setting	NCCN [76]	NANETS [77]	ENETS [78]	ESMO [79]
Adjuvant	Stage IIIA typical carcinoid: surveillance Stage IIIA atypical carcinoid: surveillance or adjuvant chemotherapy ± radiotherapy	No recommendations	Typical carcinoid and atypical carcinoid without nodal involvement: surveillance Atypical carcinoid with positive nodes and high proliferative index: adjuvant treatment	No recommendations
Metastatic	Stage IIIB typical carcinoid: observation or SSA or everolimus or chemotherapy or radiotherapy Stage IIIB atypical carcinoid: chemotherapy or radiotherapy ± chemotherapy Stage IV typical carcinoid with low tumor burden: surveillance or SSA Stage IV typical carcinoid with high tumor burden or progressive typical or atypical carcinoid: surveillance or SSA or everolimus or PRRT or chemotherapy	Carcinoid with low tumor burden and no evidence of progression: SSA or PRRT Progressive carcinoid: SSA + IFN-α No consensus on the role of chemotherapy and targeted agents	Carcinoid with low proliferation index and somatostatin receptor expression: SSA Progressive carcinoid: everolimus or chemotherapy or locoregional therapies. No consensus on PRRT	Low proliferating, functional, symptomatic carcinoid: SSA or IFN-α Non-functioning carcinoid: SSA or PRRT (if tumors overexpress somatostatin receptors) or everolimus or locoregional therapies or chemotherapy

NCCN, National Comprehensive Cancer Network; *NANETS*, North American Neuroendocrine Tumor Society; *ENETS*, European Neuroendocrine Tumor Society; *ESMO*, European Society for Medical Oncology; *SSA*, somatostatin analog; *PRRT*, peptide receptor radionuclide therapy; *IFN*, interferon

Although generally intriguing in their results, retrospective series do not allow to draw firm conclusions on the efficacy of neoadjuvant therapy in panNETs, and future research is therefore needed to define the exact role of preoperative chemotherapy in patients with locally advanced or oligometastatic panNETs.

The role of chemotherapy in midgut NETs

Chemotherapy plays a minor role in the treatment of well-differentiated midgut NETs, probably as a result of their indolent proliferative kinetics. Both randomized and nonrandomized studies have assessed the efficacy of cytotoxic agents in patients with midgut carcinoids. A phase III ECOG study [54] randomized 64 patients with progressive metastatic NETs to receive STZ/5-FU or IFN-α. Only one partial response was observed among the 23 patients with midgut NETs treated with chemotherapy, and no significant differences were shown between the two study groups in terms of both PFS and OS. Similarly, no survival benefit was observed in the chemotherapy arm of a randomized phase II study comparing STZ/doxorubicin plus IFN-α with IFN-α alone in 23 patients with NETs of different primary sites including 11 midgut tumors [55]. Consistently, in a randomized phase II/III study [56] investigating the combination of 5-FU and doxorubicin versus STZ/5-FU in 176 patients with advanced NETs of prevalently midgut origin, the response rate was 16% in both treatment arms, in the presence of a median PFS of only 4.5 and 5.3 months respectively.

Among nonrandomized studies, both prospective trials and retrospective series have consistently shown the negligible activity of single-agent chemotherapy in midgut NETs. While treatment with carboplatin did not result in any radiographic response [57], monotherapy with taxanes led to modest ORRs [58, 59]. Similarly, DTIC has been investigated in a series of 56 patients with NETs of different primary sites including 28 midgut carcinoids, and an ORR up to 20% has been reported [60]. A response rate of 8% has been also described with DTIC in patients with extra-pancreatic NETs progressive to a prior chemotherapy regimen [56]. While highly effective in panNETs, treatment with temozolomide-based regimens has been associated with poor responses in midgut NETs [33, 34, 42]. When combined with the VEGF-inhibitor bevacizumab, capecitabine induced partial responses in the 18% of 49 patients with gastrointestinal NET, leading to a promising median PFS of approximately 23 months [61]. However, a response rate of only 11% has been reported in a phase II study of octreotide, bevacizumab, and metronomic capecitabine enrolling 26 patients with extra-pancreatic NET, in the presence of a median PFS of 14 months [62]. In a retrospective series including 19 patients with gastrointestinal NET, treatment with oxaliplatin-based regimens induced an ORR of approximately 25% [50].

To date, there is no evidence of survival benefit deriving from chemotherapy in patients with intestinal NET. Therefore, both ENETS [63] and NANETS [64] guidelines do not recommend cytotoxic agents for well-differentiated midgut carcinoids. Systemic chemotherapy might be considered in patients with highly

proliferating intestinal NETs of aggressive clinical behavior, or in those patients who have exhausted both standard and investigational therapy options.

The role of chemotherapy in BP-NETs

Well-differentiated NETs of the lungs comprise low-grade (< 2 mitoses/2 mm^2) typical carcinoids and intermediate-grade (2–10 mitoses/2 mm^2) atypical carcinoids [5]. At present, only low-quality evidence guides the therapeutic management of well-differentiated BP-NETs, with the mTOR inhibitor everolimus being the only drug formally approved for these malignancies. Different cytotoxic agents, either alone or in combination, have been tested in patients with metastatic BP-NETs, often in the context of statistically underpowered studies retrospectively enrolling heterogeneous patient population. In this scenario, both etoposide-, temozolomide-, and oxaliplatin-containing regimens have demonstrated some activity in patients with BP-NETs, but the recommended standard therapy has yet to be determined.

In analogy with small-cell lung cancer, a number of small retrospective series [65–67] have investigated the combination of etoposide and platinum compounds among patients with typical or atypical pulmonary carcinoids, reporting an ORR of approximately 20% and a median PFS of 7 months. Additionally, in a prospective study of 18 patients with thoracic NETs, etoposide plus cisplatin induced radiographic responses in 40% of cases, with a median response duration of 9 months [68]. Temozolomide monotherapy has been investigated in a phase II study enrolling 13 BP-NETs, and induced an ORR of 31% with a DCR of 62% [32]. A similar DCR of 66% has been observed in a subsequent retrospective study enrolling 31 patients with progressive, typical, or atypical carcinoids, although the response rate was only 14% [69]. Scant data are currently available to recommend the use of temozolomide-based combinations in BP-NETs. In a retrospective study investigating temozolomide or CAPTEM in a wide spectrum of NET patients, a median PFS of 12 months was reported across 22 subjects with pulmonary carcinoids [43]. In another study of temozolomide plus bevacizumab, a median PFS of 7 months was recorded in the lung NET subgroup [34]. The antitumor activity of oxaliplatin-based regimens including FOLFOX and GEMOX has been assessed in several retrospective studies [50, 70, 71], and median PFS ranging between 8 and 19 months as well as response rates between 13 and 20% have been reported across patients with BP-NETs.

The role of adjuvant therapy in patients with typical or atypical pulmonary carcinoids is still controversial. In a retrospective analysis of 629 patients who underwent lobectomy for a typical carcinoid and were diagnosed with metastatic nodal involvement, no OS benefit was noted among subjects who received adjuvant chemotherapy as compared with those who underwent surveillance only [72]. Similarly, no survival advantage has been recently reported in three separate retrospective series of patients with atypical carcinoids with or without nodal disease [73–75]. As result of the lack of prospective data, different recommendations are currently provided by scientific guidelines for the use of cytotoxic agents in patients with BP-NETS in either the adjuvant or metastatic setting (Table 2). As a rule of thumb, adjuvant chemotherapy might be considered in pulmonary

carcinoids with atypical morphology, large size, high proliferation rate, and nodal metastases. On the other hand, systemic chemotherapy can be proposed to patients with clinically aggressive, rapidly progressing, and/or bulky disease.

Personalized medicine and patient selection

With multiple therapeutic options available, treatment tailoring has become of utmost importance in patients with NETs. In this context, both clinical, pathological, and molecular predictors of response to chemotherapy have been explored in recent years, but only a few of them have been validated prospectively in clinical trials. Cytotoxic agents have consistently shown substantial antitumor activity in panNETs, with modest and negligible efficacy in foregut and midgut carcinoids respectively. In addition to the pancreatic primary site, the pace of disease, the presence of symptoms, the entity of the tumor burden, the widespread rather than unifocal progression of disease, the positivity of ^{18}FDG-PET, and, most importantly, the need for cytoreduction rather than tumor stabilization should orient the physician towards the choice of chemotherapy instead of somatostatin analogs or targeted agents.

Among pathologic features, tumor grade as measured by mitotic rate or Ki-67 proliferative index is commonly regarded as a biomarker of response to chemotherapy, although in the absence of robust evidence. In a retrospective series of 173 patients with NETs who received chemotherapy, the response rate increased with grade, being 6% in G1 tumors, 24% in G2 tumors, and 43% in G3 tumors [80]. Similarly, in a study of 70 patients with G3 panNETs or panNECs, chemotherapy outcomes were significantly superior in poorly differentiated neoplasms, with the loss of Rb predicting response to platinum-based combinations in the panNEC cohort [81]. However, no correlation between tumor grade and objective response rate has been noted in other retrospective studies enrolling patients with panNETs treated with TEM-, STZ-, or platinum-based regimens [21, 37, 82].

Contrasting data have been published so far about the expression of methylguanine-methyltransferase (MGMT) as a predictor of response to TEM in patients with panNETs [33, 37, 39, 43, 49, 83–86]. MGMT is a suicide enzyme capable of repairing the DNA damage induced by alkylators through the removal of the O^6-alkylguanine adducts (Fig. 1). While the overexpression of MGMT in midgut NETs as compared with panNETs accounts, at least in part, for the differential efficacy of alkylating agents in these neoplasms [83], it remains unclear whether there is a direct correlation between MGMT deficiency and improved outcomes following TEM in patients with panNETs. Based on current evidence, the evaluation of MGMT protein expression by immunohistochemistry, or the assessment of MGMT promoter methylation by methylation-specific PCR or pyrosequencing, should be considered only as investigational. It is currently unknown whether alternative mechanisms of TEM resistance including the activation of the mismatch repair system or of the poly(ADP)-ribose polymerase (PARP) pathway might predict the efficacy of chemotherapy in NETs [87].

Evidence on additional molecular predictors of response to chemotherapy in patients with NETs is limited. In a retrospective analysis of 19 patients with panNETs treated with 5-FU-based regimens, the overexpression of dihydropyrimidine dehydrogenase (DPDH) was associated with improved ORR [88]. The activation of the alternative lengthening of telomeres (ALT) pathway has been recently investigated as potential biomarker of response to TEM in panNETs, but with inconclusive results [37].

Conclusions and future directions

Cytotoxic chemotherapy has an established role in the management of well-differentiated panNETs, while its relevance in midgut carcinoids and BP-NETs is still debated. So far, no studies have prospectively compared STZ-containing regimens versus TEM- or platinum-based combinations in patients with panNETs and therefore no chemotherapeutic protocol can be proposed as standard at present. Moreover, there are no studies comparing cytotoxic drugs versus targeted agents, and validated molecular guides of treatment selection are currently lacking. While there is preliminary evidence that concurrent chemotherapy can enhance the antitumor activity of PRRT [47, 89], there are no data to support the long-term safety of this approach, particularly in terms of AML/MDS induction. Future research is needed to properly position cytotoxic agents within the therapeutic algorithm of NETs, and the identification of molecular biomarkers of response is key for treatment tailoring and outcome optimization. Given the ability of chemotherapy to induce the emergence of new mutations and consequently neoantigens [90•], immune checkpoint blockade could be a promising option in patients with well-differentiated NETs who received cytotoxic agents, thus acquiring an elevated tumor mutational burden.

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Compliance with Ethical Standards

Conflict of Interest
Mauro Cives has received compensation from Ipsen for service as a consultant. Eleonora Pelle' declares that she has no conflict of interest. Davide Quaresmini declares that he has no conflict of interest. Barbara Mandriani declares that she has no conflict of interest. Marco Tucci declares that he has no conflict of interest. Franco Silvestris declares that he has no conflict of interest.

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.

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