Targeted and Other Non-receptor-mediated Therapies

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Sara Cingarlini, Chiara Trentin, Elisabetta Grego and Giampaolo Tortora

12.1 Introduction

Neuroendocrine neoplasms (NENs) are a relatively rare form of cancer whose incidence has sharply increased in the last decade. The diagnosis and treatment of these tumors have evolved in parallel. The recent 2010 WHO classification started a nosological (r)evolution based on a clearer distinction between: (1) neuroendocrine tumor and carcinoma and (2) grading and staging. Moreover, only a few months ago, the FDA approved everolimus and sunitinib for daily clinical use in patients with advanced "well/moderately" differentiated pancreatic NENs (PanNENs) [1].

National databases and data collected by referral centers have shown that gastro-entero-pancreatic (GEP)-NENs are most frequently located in the jejunum/ileum and pancreas, with a relative incidence of 16–29% and 31–34%, respectively. Moreover, they are characterized by higher loco-regional and distant metastatic spread; with an out-of-organ spread rate of 71–89% and 54–86%, respectively, making them the predominant NENs in oncological/non-surgical series [2].

In addition to the biological heterogeneity of NENs, the rarity of the disease and the paucity of related series have been problematic for the quality of clinical trials, such that interpretation of the results is often challenging. A recent survey of studies published between 2000 and 2010 reported six phase III and 34 phase II trials, the majority of which (78%) were single-arm studies, often including more than one tumor type (43%). Furthermore, tumor differentiation and Ki67 index were reported in only 37% and 12% of the ana-

G. Tortora (✉)
Department of Medical Oncology, "G.B. Rossi" University Hospital, Verona, Italy
e-mail: giampaolo.tortora@univr.it

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lyzed trials, respectively [3]. As a further methodological drawback, the results of these studies were frequently ambiguous, due to the lack of routine evaluation of disease status at the time of enrollment. In the largest published series of NENs/carcinomas (NEN/Cs) treated with ^{177}Lu-DOTA-TATE, only 43% of patients had documented progressive disease (PD) before peptide receptor radionuclide therapy (PRRT) enrollment [4]. Not even in the PROMID study, which evaluated the ability of somatostatin analogues (SSAs) to control the growth of advanced midgut well-differentiated NENs, was PD a required inclusion or stratification criterion. Disease status was reported in only 50% of the published trials and only 20% of them included progressive cases at baseline [5].

Unlike patients with other types of cancers, those with NENs can benefit from a multi-disciplinary approach, including in the metastatic setting. Strategies including surgery for loco-regional or metastatic disease, even if only for tumor debulking purposes, have been proven to confer a survival advantage in some patients. Based on a SEER retrospective survival analysis of 728 patients with PanNENs, surgery for locally advanced and metastatic disease is advocated in selected cases due to the significant survival advantage: 129 vs. 64 months for resected vs. non-resected localized metastatic disease, and 60 vs. 31 months for distant metastatic disease [6]. In addition to aggressive approaches to the management of advanced NENs, nowadays the primary need is to determine sequential strategies that optimize the use of all therapeutic options. Randomized head-to-head trials comparing different therapeutic strategies are lacking, while indirect and retrospective comparisons of published data are potentially misleading.

Another highly current topic is the effectiveness of response evaluation in patients receiving the new medical therapeutic options. While the efficacy of chemotherapeutic regimens can, in most cases, be properly assessed according to WHO or RECIST parameters, the molecular targeted agents require different criteria, as tumor size measurements according to RECIST could underestimate the real clinical benefit of these tailored drugs. Perfusion/functional computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and positron emission tomography (PET) with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) are emerging as novel resources for dimensional and/or functional imaging of these tumors. Although still limited in numbers, the experiences described to date with perfusional CT scans are encouraging. In 22 patients with advanced carcinoid tumors and liver metastases, bevacizumab treatment significantly reduced tumor blood flow and volume compared to baseline and to the untreated controls. However, due to the limited number of patients, a significant correlation with standard outcome parameters could not be determined [7]. In a larger series of patients with advanced low- to intermediate-grade NENs, the combination of bevacizumab and everolimus resulted in a partial remission (PR) rate of 26%. A functional CT (fCT) evaluation showed a significant association between standard RECIST criteria and fCT parameters (baseline permeability surface, blood flow mean transit time,

intralesional blood flow and volume) in responding patients [8].

Clearly, these novel therapeutic approaches demand a new analytical approach, one that integrates a wide range of clinical and imaging skills, resources and perspectives in disease evaluation and the development of unambiguous guidelines regarding the treatment of these patients.

12.2 Chemotherapy

In contrast to the low chemosensitivity of other NENs, PanNENs show moderate/good responsiveness to some antiblastic agents. In a literature search of publications since 1980, we collected 35 papers (published in extenso) and nine abstracts addressing the issue of chemotherapy for PanNENs. Among the papers, 14 were retrospective surveys (mono- or poly-centric) and 21 were prospective studies (of which only three were randomized). Ten were "PanNEN-dedicated" and ten others were selected because they included at least ten cases of PanNENs; seven studies also enrolled patients with poorly differentiated disease. Mono- and poly-chemotherapy were evaluated in six and 16 trials, respectively, either as a single-arm study or in the context of a randomized trial. Regarding progressive disease, in three of the 20 studies (15%) it was among the inclusion criteria, while in six of the 20 (30%) it specifically was not. In the remaining studies, no such information was provided. The great majority of enrolled patients had undergone previous treatment, most of them with an SSA.

Single-agent chemotherapy in PanNEN was shown to have a limited role. Dacarbazin (DTIC) yielded a response rate (RR) of 26%, with a median progression-free survival (PFS) of 10 months [9]; for streptozototcin (STZ), the RR was 21–36% with a PFS of 16.5–33 months [10, 11], and with chlorzotocin (CTZ) a PR of 30% with a PFS of 17 months was reported [12]. Temozolomide was tested in a heterogeneous population of 36 patients with thoraco-abdominal NENs, including only 12 PanNENs; the global RR was 8% and PFS did not exceed 7 months [13].

In one of the first random controlled trials (RCTs) comparing mono- and poly-chemotherapy in the setting of PanNENs, STZ was tested against the combination of STZ and 5-fluorouracil (STZ/5-FU); both the RR of 36 vs. 63% and the overall survival (OS) of 16.5 vs. 26 months significantly favored the combination arm. The same study compared, in a three-arm RCT, CTZ alone, and two STZ-based regimens: STZ/5-FU and doxorubicin/STZ (ADM/STZ); the latter was significantly superior to STZ/5-FU in terms of RR, PFS, and OS (45 vs. 69%, 13 vs. 22 months, and 17 vs. 26 months, respectively) [12]. The same combination was not able to reproduce similar results in two other poly-chemotherapy single-arm retrospective studies, in which STZ/ADM resulted in a RR of 6–36%, a median PFS of 3.9–16 months, and an OS of 20.2–24 months [14-17]. Oxaliplatin, which has a moderate activity in well-/intermediate-differentiated NENs, was tested together with

capecitabine in a series of 40 patients with WD-NEN (well-differentiated neuroendocrine neoplasm) (15 PanNENs); a PR was obtained in 27% of the patients, with a median PFS of 20 months and an OS of 40 months [18]. However, when used in combination with gemcitabine, oxaliplatin did not have a similar efficacy, probably because of the limited activity of gemcitabine in this histotype [19]. The GEMOX regimen was tested in a heterogeneous group of 20 patients with thoracic, GEP, and unknown-primary NENs; (only 5 PanNENs). The overall RR was 17%, with a median PFS of only 7 months and an OS of 23.4 months [20].

Intensification with three-drug regimens has produced only a slight increase in efficacy. The attempt to intensify regimens by adding a third drug to the above-mentioned doublets, although never tested in a RCT, does not seem to lead to significant clinical improvement. Dacarbazin and cisplatinum were the most frequently tested drugs in combination with STZ/5-FU or 5-FU/ADM backbones. The RR for the triplets ranged from 19.5% to 58%; the PFS from 9.1 to 21 months, and the OS from 21 to 38 months [21-25].

The combination of temozolomide and capecitabine has shown promising results. The efficacy of this regimen was tested in 30 patients with PanNENs, yielding a PR of 70%, a median PFS of 18 months, and an OS of 92% at 2 years [26]. The encouraging activity of this doublet has a biological rationale; the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT) contributes to the resistance of tumor cells to temozolomide. As demonstrated by a recent immunohistochemistry analysis of NEN samples, 51% and 0% of pancreatic and small-intestine NENs, respectively, showed MGMT deficiency [27]. This could represent the biological basis for the higher sensitivity of pancreatic, compared to other NENs following temozolomide treatment. Whether MGMT deficiency can serve as a predictive marker of response to temozolomide warrants further studies. Similarly, the intracellular depletion of MGMT by the co-administration of capecitabine may account for the observed synergistic effect.

The most relevant features of the main chemotherapy trials are summarized in Table 12.1.

12.3 Targeted Therapies

The PI3K-Akt-mTOR pathway is a key regulator pathway in the biology of NENs [28-35] and its constitutive activation has been described in many malignancies, including these tumors. Some genetic syndromes have evidenced the role of a loss or the down-regulation of tumor suppressor phosphatase and tensin homologue (PTEN) or tuberous sclerosis 2 (TSC-2) in the constitutive activation of the PI3K-Akt-mTOR pathway. These alterations have been frequently described also in NEN tumorigenesis; 85% of PanNENs show altered levels of TSC2 and/or PTEN and in both cases the degree of down-regulation inversely correlates with prognosis, as demonstrated in a

Table 12.1 Main clinical studies with chemotherapy

Author (year)	CT (mono-CT)	Type	Total pts n°	n° PanNETs	PFS (months)	OS (months)	RR (%)
Brizzi et al. (2009) [42]	5FU (+Octreotide LAR)	NEN	29	13	22.6	NR	24.1
Ekeblad et al. (2007) [13]	TMZ	NEN	36	12	7	16	8
Ramanhatan et al. (2001) [9]	DTIC	NEN	50	50	10	19.3	26
Moertel et al. (1992) [43]	CZT	NEN	105	33	17	18	NA
Moertel et al. (1980) [10]	STZ	NEN	52	52	33	42	21
Broder et al. (1973) [11]	STZ	NEN	84	42	NA	16.5	36
	CT (doublets)						
Strosberg et al. (2011) [26]	CPT/TMZ	NEN	30	30	18	NA	70
Bajetta et al. (2007) [18]	XELOX	NEN/NEC	40	15	20	40	27
McCollum et al. (2004) [14]	STZ/DOXO	NEN	16	16	3.9	20.2	6
Delaunoit et al. (2004) [15]	DOXO/STZ	NEN	45	45	16	24	36
Fjallskog et al. (2001) [44]	CDDP/VP16	NEN/NEC	36	15	9	NA	36
Mitry et al. (1999) [45]	CDDP/VP16	NEN	12	4	2.3	17.6	9.1
Cheng et al. (1999) [17]	STZ/5FU	NEN	16	16	NA	NR	6
Moertel et al. (1992) [43]	5FU/STZ	NEN	105	34	13	17	NA
Moertel et al. (1992) [43]	DOXO/STZ	NEN	105	38	22	26	NA
Moertel et al. (1991) [46]	CDDP/VP16	NEN	45	14	4	15.5	14
Eriksson et al. (1990) [16]	STZ/DOXO	NEN	59	25	27.5	NA	NA
	CT (triplets)						
Turner et al. (2010) [21]	STZ/5FU/CDDP	NEN/NEC	82	49	9.1	31.5	38.2
Walter et al. (2010) [22]	5FU/DCZ/EPI	NEN	39	16	17	27	58
Kouvaraki et al. (2004) [23]	5FU/DOXO/STZ	NEN	84	84	18	37	39
Bajetta et al. (2002) [24]	DCZ/5FU/EPI	NEN	82	28	21	38	19.5
Rivera E et al. (1998) [25]	STZ/DOXO/5 FU	NEN	12	12	15	21	54.5

series of 72 patients with PanNENs [36]. Furthermore genome sequencing together with expression profiling has identified somatic mutations implicated in the self-maintenance of activated signaling along this pathway.

Data from clinical trials have supported the central role of the PI3K-Akt-mTOR pathway in PanNEN tumorigenesis. In the RADIANT-1 study, everolimus was administered either alone or in combination with octreotide long-acting release (LAR), if such treatment was ongoing at baseline. The primary endpoint was RR in the largest stratum of everolimus monotherapy (n = 115 patients). In these patients, the RR was 9.6% vs. 4.4% for patients in the everolimus + octreotide stratum. No conclusions could be drawn regarding possible interactions between everolimus and SSA because: (a) it was not a randomized study; (b) the number of patients in the everolimus stratum greatly exceeded that in the combination arm; and (c) the biology of the patients enrolled in the two strata differed. Specifically, in the stratum with everolimus alone, 19% of SSA-naïve patients had a syndromic tumor, including those who might have benefited from inclusion in the stratum with everolimus and SSA. PFS in the SSA + everolimus stratum was longer than in the everolimus alone stratum (16.7 vs. 9.7 months) [37]. The antitumor activity and safety of everolimus in the treatment of NENs confirmed the conclusion of a previous phase II study. This trial similarly intended to evaluate the activity of everolimus in combination with octreotide LAR in patients with advanced PanNEN. The overall RR (ORR) was somewhat higher than in RADIANT-1 (30% in the arm comprising patients treated with the same everolimus dose). However, the population differed between the studies: in the first study, the percentage of patients (34%) enrolled with stable disease was higher and a minority of them (43%) were pretreated with chemotherapy [38].

The RADIANT-3 study further explored the role of everolimus in the management of 410 patients with advanced PanNENs, in a randomized fashion against placebo. Pretreatment with chemotherapy was a stratification criteria and SSA treatment was allowed in both arms during the trial. The trial design enabled cross-over at PD, with PFS as the only suitable primary endpoint in order to evaluate clinical benefit. PR, defined according to RECIST, was obtained in 5% of the patients in the everolimus arm but 64% of patients receiving the drug experienced some degree of tumor shrinkage, compared to 21% in the placebo arm. In addition, everolimus reduced tumor proliferation, as shown by a decreased in the Ki67 index on paired re-biopsies. However, the most striking benefit following everolimus treatment was longer time to disease progression. Specifically, the adjudicated central review PFS was 11.4 and 5.4 months for the everolimus and placebo arms, respectively, resulting in a reduction of the risk of progression for the experimental arm of nearly 65%. No subgroup was disadvantaged: neither chemotherapy-pretreated patients nor those with moderately differentiated tumors. The homogeneous selection of patients with PanNENs and progressive disease together with the adequate sample size enrolled renders the results of this trial essentially unquestionable. Nonetheless, some concerns remain regarding the biology of the tumors

included in the study, since: (a) 70% of the patients had a diagnosis of PD within 3 months before enrollment and nothing is known about pre-progression disease behavior; (b) 17% of the patients had moderately differentiated tumors for which not even a median Ki67 was reported [39]. The lack of this information could make it difficult to compare this trial with others. The RR and PFS obtained with everolimus of 5% and 11.4 months, respectively, must be compared with those obtained with other strategies. PRRT with Lu-DOTA-octreotate on Octreoscan-positive PanNENs lead to RRs ranging from 36% for non-functioning pancreatic tumors to 60% for insulinomas, with a global PFS of nearly 40 months. STZ-based chemotherapy, according to a historical study, obtained an RR in 69% of PanNEN-bearing patients, with a median PFS of 22 months. Head-to-head comparisons, in the context of a phase III RCT, of the currently available therapeutic strategies are warranted.

NENs are highly vascularized tumors. High levels of VEGF expression by PanNENs is a negative prognostic factor related to higher microvessel density, a higher incidence of metastases, and a shorter PFS. Many different anti-angiogenic drugs are now available for clinical use, both as specific target agents or as pleiotropic kinase inhibitors. Bevacizumab was tested in a phase II randomized study against pegylated interferon-α (PEG-IFNα) in a population of 44 patients with carcinoids (excluding pancreas primaries) who received a stable dose of octreotide. In the bevacizumab arm, 18% of patients achieved a PR, with 77% SD in contrast to the PEG-IFNα arm, in which no PR was documented and SD was obtained in 68% of patients [8]. The results of many trials, including bevacizumab in combination with either chemotherapy or other targeted agents, in patients with advanced, are awaited. A prospective randomized phase III trial testing bevacizumab + octreotide LAR vs. IFNα + octreotide LAR, as well as other phase II single-arm clinical studies (TMZ + bevacizumab, CAPOX + bevacizumab, FOLFOX + bevacizumab, everolimus + bevacizumab) are ongoing.

Sunitinib was also tested as anti-angiogenetic multi-target agent in NENs. The first experience, in a single-arm phase II trial, showed promising results. In that study, 109 patients with advanced NENs (66 PanNENs and 41 carcinoids) were evaluated. A PR was obtained in 16.7% of the PanNEN patients, with a median PFS of 7.7 months; among those with carcinoids, the RR was 2.4%, with a PFS of 10.2 months [40]. The assumed major clinical benefit of sunitinib in the subgroup of patients with PanNENs led to a phase III study in which only patients with advanced PanNENs were enrolled. The 171 patients were randomly assigned to receive sunitinib (37.5 mg/day) or placebo together with best supportive care. Patients with PD in the placebo arm were allowed to enter an open-label sunitinib extension protocol; thus, the primary end point was necessarily PFS, as in the everolimus registrative phase III study. Noteworthy baseline characteristics of the enrolled patients were: 22% with tumors having a Ki67 > 10% and 66% pretreated with chemotherapy in the experimental arm. Patients in both arms were allowed to receive SSAs according to the investigators' discretion. Both these percentages were well-balanced

in the placebo arm. After assessment of the data on 154 patients, the safety monitoring committee recommended discontinuation of the trial because of the large number of deaths and serious adverse events in the placebo group. At that time point, a RR of 9.3% and 0% were recorded in the experimental and placebo arms, respectively. A statistically significant difference in PFS between the two arms was also determined (11.4 vs. 5.5 months). Both subgroups of patients benefited from sunitinib but the hazard ratio for progression in the experimental arm compared to placebo seemed to favor patients with a Ki67 index ≤5 % [41].

The most relevant features of the main trials with target agents are summarized in Table 12.2.

Table 12.2 Main clinical studies with targeted agents

Author (year)	Therapy	Type	Total pts (n)	Pan NENs (n)	PFS (months)	OS (months)	RR (%)
Yao et al. (2011) [39]	Everolimus	NEN	410	207	11	NR	5
Yao et al. (2010) [37]	Everolimus	NEN	160	115	9.7	24,9	9.6
Pavel et al. (2011) [47]	Everolimus + Oct LAR	NEN	216	5	16.4	NA	NA
Yao et al. (2008) [8]	Everolimus 5/10 + Oct LAR	NEN	30	29	12.5	NR	13
Duran et al. (2006) [48]	Temsirolimus	NEN	37	15	10.6	NR (86.5%) at 2 ys	6.7
Raymond et al. (2011) [41]	Sunitinib	NEN	171	86	11.4	NA	7
Deeks et al. (2011) [49]	Sunitinib	NEN	86	86	12.6	30,5	9.3
Barriuso et al. (2010) [50]	Sunitinib	NEN	40	28	12	NR	7
Kulke et al. (2008) [40]	Sunitinib	NEN	109	66	10.5	NA (83.4%) at 2 ys	17 17
Castellano et al. (2010) [52]	Sorafenib + Beva	NEN	44	13	10	NA	16.7
Yao et al. (2008) [8]	Oct LAR + Beva /IFN PEG	NEN	44	0	16.5	NA	NA
Hobday et al. (2007) [53]	Sorafenib	NEN	93	43	NA	NA	7.5
Kulke et al. (2006) [54]	Temozolamide + Beva	NEN	34	18	NA	NA	NA

NA, Not assessed; *NR,* not reached; *NEN,* neuroendocrine neoplasm.

Recent developments in the setting of NENs underline some of the most rapidly evolving areas in the oncologic panorama. Although univocal and shared treatment strategies have yet to be defined, the growing number of currently available drugs holds promise as the basis of a firmer and more successful therapeutic future.

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